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THE INFLUENCE OF NITROGEN PEROXIDE ON THE LOW TEMPERATURE AUTO-IGNITION OF DIETHYL ETHER

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(Communicated by K. Venkataraman)

Summary

The results indicate that the influence is similar to that previously recorded with *n*-butane-oxygen mixtures, in that the acceleration of the direct oxidation indicated by a decrease in the minimum pressures for ignition is observed simultaneously with the inhibition of the cool flame reaction, characterized by an increase in the induction lag.

Chemical analysis shows that the concentration of acetaldehyde in the products of the pre-cool flame reaction decreases with an increase in the nitrogen peroxide additions and provides additional support to the view that acetaldehyde is of primary importance in the formation of cool flames.

Introduction

Previous experiments on the spontaneous ignition of propane, *n*-butane or acetaldehyde-oxygen media have shown (*cf.* Kane, 1939) that at temperatures between 200-400° C., involving a two-stage ignition, NO_2 additions have a composite influence, consisting in a simultaneous inhibition of the reactions leading to cool flames and a promotion of the direct oxidation of the combustible. With propane, the inhibition was indicated by an increase, in the cool flame and total time lags, and the minimum pressures for the two-stage ignitions with NO_2 additions, up to a critical concentration of about 3·25 per cent. With greater NO_2 additions, an overall promoting influence was observed, since the cool flames were no longer observable and the mixtures ignited abruptly at greatly reduced minimum pressures and shorter time lags. With *n*-butane these abrupt ignitions were not observed, but lower minimum pressures for the two-stage ignitions even with small NO_2 additions indicated a greater promotion of the direct oxidation than with propane. The inhibition was again marked by a continuous increase of the time lags with NO_2 additions and elimination of cool flames with more than 5 per cent.

NO_2. Similar results were obtained with acetaldehyde, the inhibition being greater than either with propane or *n*-butane.

It was a matter of interest to investigate whether NO_2 additions would have a similar composite influence with other inflammable materials, such as di-ethyl ether. Ether resembles higher hydrocarbons very closely in that it exhibits well-developed cool flames and two-stage ignitions in the lower temperature region (200-400° C.) during spontaneous ignition (*cf.* Townend and Chamberlain, 1937), and also when ignition is induced artificially by means of a heated wire at room temperature and high enough pressure (Hshieh and Townend, 1939). Further, ether is known to peroxidise in air, even at room temperature and large amounts of higher aldehydes are found associated with the products obtained from a " stationary " cool flame, maintained in an ether-oxygen mixture (Maccormac and Townend, 1940).

The present paper records the results of experiments carried out with di-ethyl ether. Hitherto Kane had restricted his experiments to a study of the influence of NO_2 additions on two-stage ignitions only; now it has been possible to extend the observations to cool flames as well, since the time lags at the minimum pressures for the propagation of cool flames are not inconveniently long with ether-oxygen mixtures. In addition, a few analyses of the intermediate products formed prior to ignition have been carried-out to determine the variation in the aldehyde content due to NO_2 additions, in view of the suggestion of Kane that acetaldehyde is of primary importance in the formation of cool flames and two-stage ignitions.

Experimental

The minimum pressures for spontaneous ignition were determined by a static method, in which the prepared inflammable mixtures were admitted into an evacuated reaction vessel maintained at the requisite temperature. The apparatus and the procedure were similar to those previously described by Kane (*loc. cit.*). The inflammable mixtures with oxygen were prepared and stored at room temperature (28-30° C.), the di-ethyl ether employed being rendered free from peroxides by distillation over sodium.

At first, the limits of propagation of spontaneously ignited cool flames and two-stage ignitions were determined experimentally. Curves A and B (Fig. 1) were obtained by plotting the minimum pressures for cool flames at 200 and 206° C., respectively, against mixture composition expressed as per cent. ether in oxygen. Cool flames could be observed with mixtures containing between 23 and 70 per cent. of ether, within the area bounded

by the V-shaped curves. The time lags in seconds for the limit mixtures have been marked along the curves and it may be seen that both the minimum pressures and the time lags decrease with an increase in the experimental temperature.

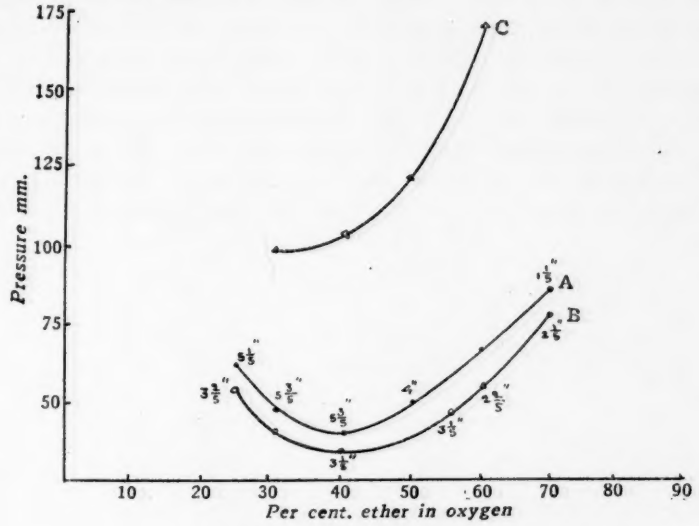

FIG. 1. Cool flame limits

Curves A and B refer to limits at 200° and 206° C.

With any particular mixture, at a critical pressure considerably above the minimum required for the propagation of cool flames, a rapidly moving yellow-flame appeared after a short interval, in the products left behind by the cool flame. Curve C (Fig. 1), refers to the variation in the minimum pressures for these two-stage ignitions, with a change in the mixture composition at a temperature of 200° C. The ignitions were accompanied by a sudden development of pressure, and increased in violence with an increase in the oxygen content of the mixtures. The curve was not extended, therefore to mixtures containing less than 30 per cent. ether.

In order to ensure that the available time-lag exceeded one second, all experiments were carried out at a temperature of 200° C., with NO_2 additions to mixtures containing 40, 50 and 60 per cent. ether.

Results

Two-stage ignitions—Minimum pressures.—Curve A (Fig. 2), indicates the variation in the minimum pressure for ignition (P = partial pressure of

combustible + oxygen, in mm.) for the 40 per cent. ether mixture, with increasing NO_2 additions. Small NO_2 additions decrease the minimum pressure considerably, the influence being at a maximum with about 3·25 per cent. of NO_2. With further NO_2 additions, the minimum pressures again increase indicating an anti-catalytic influence probably due to the neutralization of active centres by mutual reaction. Curves B and C, which refer to mixtures containing 50 and 60 per cent. ether, respectively, show a similar behaviour and indicate in general that small NO_2 additions promote the normal ignition of ether, but an inhibiting influence becomes operative when the NO_2 addition exceeds 3·5 per cent. Cool flames preceding the ignitions became less intense as the NO_2 additions to the mixture increased and could not be observed at all, when the latter exceeded 5 per cent.

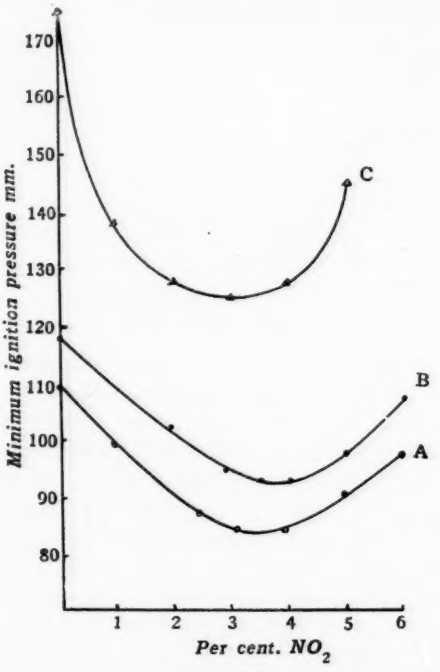

FIG. 2

Curves A, B and C denote the limits for the two-stage ignition for 40, 50 and 60 per cent. ether-oxygen mixtures respectively at 200° C.

Time lags.—Curves A, B and C (Fig. 3) illustrating the variation in time lag with NO_2 addition, at a constant initial pressure P (ether + oxygen), show

a definite inhibition of the two-stage ignitions. For instance, curve A shows that for the 40 per cent. ether mixture the time lag increases continuously from 1½ seconds for the undiluted mixture to 9½ seconds with 5 per cent. NO_2. The 60 per cent. ether mixture behaved similarly (curve C), while the inhibiting influence was most marked with the 50 per cent. ether mixture,

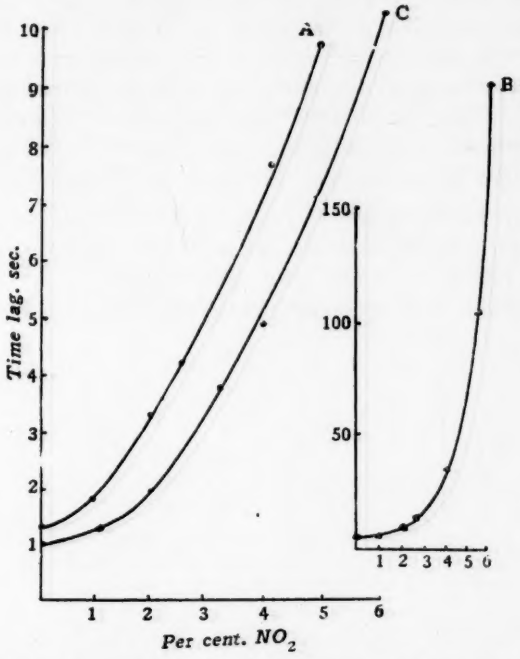

FIG. 3. Time lags for two-stage ignitions with NO_2 additions at constant ignition pressure
Curves A, B and C refer to 40, 50 and 60 per cent. ether mixtures, at P = 109, 118 and 170 mm. respectively at 200° C.

the time lag increasing from 2 to 204 seconds for 6 per cent. NO_2 addition. It may be mentioned that similar results have been obtained by Forsyth and Townend (in private communication) during experiments on ignitions initiated by a hot wire and therefore the observations recorded above are of general application so far as ether is concerned.

Cool flames—Minimum pressures.—The minimum pressures for cool flames with NO_2 additions, are given in Table I.

TABLE I

Per cent. NO_2	0	1	2	2·5	3	4	5	6
			Minimum pressures in mm.					
40 per cent. ether ..	40	39	39	38	37	44	44	44
50 „ „ ..	52	49	50	..	53	53	..	..

Since the accuracy of the minimum pressure determinations is of the order ± 1 mm. it may be inferred from Table I that NO_2 additions up to 3 per cent. hardly affect the minimum pressure, while with greater addition the pressures are raised slightly, indicating an inhibition of the reaction.

Time lags.—It may be seen from curves A, B and C (Fig. 4) that at constant ignition pressure, the time lags are distinctly longer with NO_2 additions, indicating an inhibition of the cool flame reaction. As with two-stage ignitions, the inhibition is most marked with the 50 per cent. ether mixture.

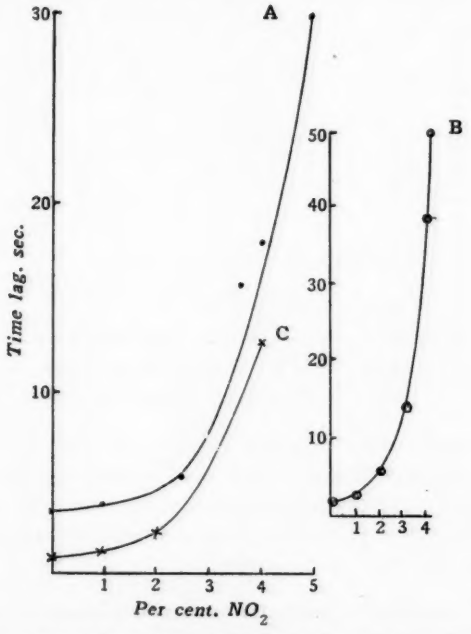

FIG. 4. Time lag at cool flame limits with NO_2 additions at constant ignition pressure
Curves A, B and C refer to 40, 50 and 60 per cent. ether mixtures, at P = 60, 102 and 60 mm. respectively at 200° C.

Estimation of aldehydes.—In order to estimate the amount of aldehydes formed in the intermediate products prior to the propagation of cool flames, samples of gas were withdrawn at definite intervals of time by allowing the reaction mixture to expand into an evacuated bulb cooled with solid carbon dioxide. The sample was shaken with distilled water, and aldehydes determined colorimetrically with Schiff's reagent. Formaldehyde was found to be absent and it was assumed that with diethyl ether, the higher aldehydes would consist mainly of acetaldehyde.

Curves A A′ and B B′ (Fig. 5) at a time lag of 2 and 4 seconds and initial mixture pressures of 90 and 78 mm. respectively, indicate that in all the experiments there is a progressive diminution in the aldehyde content with NO_2 additions up to 6 per cent.

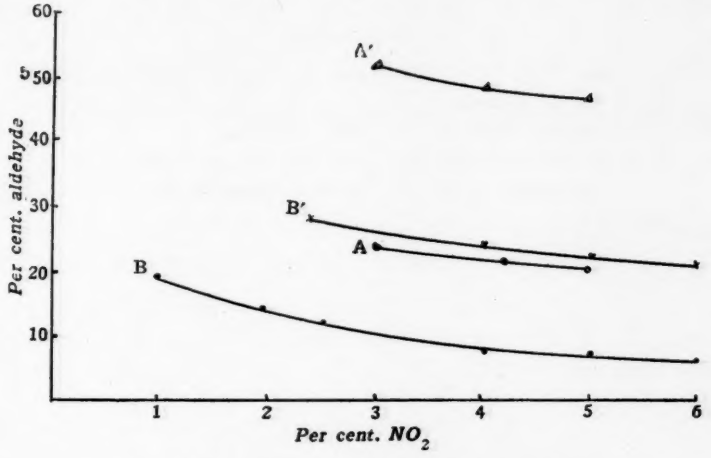

FIG. 5. 40 per cent. ether-oxygen mixtures at 200° C.

Curves A and A′ refer to a mixture pressure (combustible + oxygen) at P = 90 mm. at 2 and 4 seconds respectively. Curves B and B′ at P = 78 mm. at 2 and 4 seconds respectively

Discussion

The results obtained with di-ethyl ether correspond very closely with the previous observations with *n*-butane and acetaldehyde in that with small NO_2 additions, a promotion of the direct oxidation is denoted by lower minimum pressures for two-stage ignitions, and an inhibition of the cool flames by an increase in the time lags. A specific inhibition of the cool flames is further demonstrated since the minimum pressures for

cool flames are hardly affected, while the time lags are considerably increased with NO_2 additions.

The important rôle played by acetaldehyde as a promoter of the low temperature ignition of paraffinic hydrocarbons and allied fuels is well known. Since the inhibition of the cool flame reaction of acetaldehyde is greatest in the presence of NO_2 (*cf.* Kane), it may be expected that in the intermediate products the concentration of acetaldehyde would decrease with successive NO_2 additions to the combustible media. Such a result has been observed now with ether-oxygen mixtures and gives additional support to the view that acetaldehyde is primarily involved in the formation of cool flames.

The authors desire to express their thanks to the University of Bombay, for the award of a " Singhanee Fellowship for pure research " to one of us (M.G.P.).

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SOME CONGRUENCE THEOREMS

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(Communicated by Dr. A. Narasinga Rao)

1. In two papers entitled "A Theorem on Congruence" I have proved the theorem :

if p be an odd prime, then

$$\sum_{i=1}^{p-1} n^{p-1} - p - (p-1)\,! \equiv 0 \pmod{p^2}$$

and its generalization:

if $n_1, n_2, \ldots, n_\phi$ $[\phi = \phi(m)]$ be a reduced residue system, (mod m), then

$$\sum_{r=1}^{\phi} n_r^{\phi} \pm \phi.\ n_1 n_2 \ldots n_r \equiv 0 \pmod{m^2},$$

where the positive sign is to be chosen when $m = 4$, p^n *or* $2p^n$, p being an odd prime, and the negative sign when m has any other value.

The first of these results has been previously obtained by M. Lerch in a paper entitled "Zur Theorie des Fermatschen Quotienten" by a method which is practically the same as that employed to obtain the second result. In the same paper Lerch proves a number of other Congruence relations some of which are similar to those proved in this paper.

The results of this paper are obtained by the same method as that by which the second of the above results was obtained.

2. Let the numbers p_i $(i = 1, 2, \ldots, k)$ satisfy the following conditions :

$$p_i^i \equiv r_i \pmod{m} \quad (i = 1, 2, \ldots k)$$

$$p_1 p_2 \ldots p_k \equiv a \pmod{m}.$$

Then we have

Theorem 1.

$$\left(1 - k + \sum_{i=1}^{l} p_i^i/r_i\right) \prod_{i=1}^{k} r_i \equiv a^{l-1} \left\{(1-l)\,a + l \prod_{i=1}^{k} p_i\right\}, \pmod{m^2}$$

PROOF :

$$\prod_{i=1}^{k}(x+p_i^l) = \prod_{i=1}^{k}(x+r_i+p_i^l-r_i)$$

$$\equiv \left[1+\sum_{i=1}^{k}\frac{p_i^l-r_i}{x+r_i}\right]\prod_{i=1}^{k}(x+r_i), \pmod{m^2}.$$

Putting $x=0$ we get

$$\left(\prod_{i=1}^{k}p_i\right)^l \equiv \left[1-k+\sum_{i=1}^{k}p_i^l/r_i\right]\prod_{i=1}^{k}r_i, \pmod{m^2}.$$

But

$$\prod_{i=1}^{k}p_i = \lambda m + a$$

λ being an integer, so that

$$\{\Pi p_i\} = (\lambda m+a)^l$$

$$\equiv a^l + l\lambda m\, a^{l-1}, \pmod{m^2}$$

$$\equiv a^l(1-l) + l\, a^{l-1}\prod_{i=1}^{k}p_i, \pmod{m^2},$$

whence we get the required result.

THEOREM 2. If e be the exponent of p modulo the prime m,

$$(p^{e^2}-1)/(p^e-1) \equiv (-1)^{e-1}\, e\, p^{\frac{e(e-1)}{2}}, \pmod{m^2}.$$

PROOF : Take $p_i \equiv p^{i-1}$ and $k=l=e$ in Theorem 1. Then

$$\Pi p_i = p^{\frac{(e-1)e}{2}} \equiv (-1)^{e-1} \pmod{m},$$

so that $a=(-1)^{e-1}$, and $r_i=1$.

Therefore

$$1-e+\frac{p^{e^2}-1}{p^e-1} \equiv 1-e+(-1)^{e-1}\, e\, p^{\frac{e(e-1)}{2}}, \pmod{m^2}$$

from which we get the required result.

Let $\left(\frac{i}{p}\right)$ be Legendre's symbol equal to $+1$ if i be a quadratic residue of the prime p and to -1 if i be a quadratic non-residue of p. Then we have

THEOREM 3. If p be prime and x be prime to p,

$$(x^{(p-1)^2}-1)/(x^{p-1}-1) \equiv \left(\frac{x}{p}\right)(p-1)\, x^{(p-1)(p-2)/2}, \pmod{p^2}.$$

PROOF : Take $p_i = x^{i-1}$ and $k = l = p-1$ in Theorem 1. Then

$$\prod_{i=1}^{p-1} p_i = x^{(p-2)(p-1)/2} \equiv \left(\frac{x}{p}\right)^{p-2} \equiv \left(\frac{x}{p}\right), \pmod{p},$$

so that $a = \left(\frac{x}{p}\right)$.

Also, by Fermat's Theorem, $r_i = 1$. Therefore

$$1-(p-1)+\frac{x^{(p-1)^2}-1}{x^{p-1}-1} \equiv 1-(p-1)+\left(\frac{x}{p}\right)(p-1)\prod_{i=1}^{p-1} x^{i-1}, \pmod{p^2},$$

whence the theorem follows.

THEOREM 4. If p be an odd prime, then

$$\sum_{i=1}^{p-1}\left(\frac{i}{p}\right) i^{\frac{p-1}{2}} \equiv \frac{p-1}{2}\left\{1-(p-1)!\right\} \pmod{p^2}.$$

PROOF : Take $p_i = i$, $l = \frac{p-1}{2}$, $k = p-1$ in Theorem 1.

Then we have

$$p_i^l \equiv \left(\frac{i}{p}\right) \pmod{p}$$

and

$$\prod_{i=1}^{p-1} p_i \equiv -1 \pmod{p}, \text{ by Wilson's Theorem.}$$

so that $r_i = \left(\frac{i}{p}\right)$, $a = -1$ and $\Pi r_i = (-1)^{\frac{p-1}{2}}$.

Therefore

$$\left[1-(p-1)+\sum_{i=1}^{p-1}\left(\frac{i}{p}\right) i^{\frac{p-1}{2}}\right](-1)^{\frac{p-1}{2}} \equiv$$

$$(-1)^{\frac{p-1}{2}}\left[\left(1-\frac{p-1}{2}\right)-\frac{p-1}{2}(p-1)!\right], \pmod{p^2}.$$

From this we get the required result.

THEOREM 5. If p be an odd prime and α runs through the quadratic residues of p, then

$$\Sigma \alpha^{\frac{p-1}{2}} + (-1)^{\frac{p-1}{2}}\frac{p-1}{2}\Pi a \equiv 0 \pmod{p^2}.$$

PROOF : In Theorem 1 take the p_i's to be the α's so that

$$k = \frac{p-1}{2}, \text{ and } l = \frac{p-1}{2}. \text{ Then}$$

$$\alpha^{\frac{p-1}{2}} \equiv 1 \pmod{p}$$

and

$$\Pi \alpha \equiv (-1)^{\frac{p+1}{2}} \pmod{p}.$$

Therefore

$$\left(1-\frac{p-1}{2}+\Sigma\, a^{\frac{p-1}{2}}\right) \equiv 1-\frac{p-1}{2}+(-1)^{\frac{p+1}{2}}\frac{p-1}{2}\,\Pi\, a \pmod{p^2}$$

from which the theorem follows.

In a similar manner we may prove

THEOREM 6. If β runs through the quadratic non-residues of an odd prime p, then

$$\Sigma\,\beta^{\frac{p-1}{2}}+(-1)^{\frac{p-1}{2}}\frac{p-1}{2}\,\Pi\,\beta \equiv 0 \pmod{p^2}$$

From Theorems 4, 5 and 6 we get

THEOREM 7. If α, β run through the quadratic residues and the quadratic non-residues respectively of an odd prime p, then

$$(p-1)\,! \equiv 1+(-1)^{\frac{p-1}{2}}\,[\Pi\,\alpha-\Pi\,\beta], \pmod{p^2}.$$

3. We require the following

Lemma.—Let $a_1, a_2, \ldots, a_k$ be all divisible by m. Then

$$(1-a_1)\,(1-a_2)\ldots.(1-a_k) \equiv 1-\sum_{i=1}^{k} a_i \pmod{m^2}.$$

THEOREM 8. If p be an odd prime,

$$\left\{1\,!\;2\,!\;3\,!\ldots.(p-1)\,!\right\}^2 \equiv \frac{(-1)^{\frac{p-1}{2}}}{p-1}, \mod p^2.$$

PROOF : We know that

$$1+\frac{(-1)^{i-1}}{(p-i)\,!\,(i-1)\,!} \equiv 0 \pmod{p} \quad (i=1, 2, \ldots, p-1).$$

Take $a_i = 1+\dfrac{(-1)^{i-1}}{(p-i)\,!\,(i-1)\,!}$, $k=p$ in the lemma.

Then we have

$$\prod_{i=1}^{p} \frac{(-1)^i}{(p-i)\,!\,(i-1)\,!} \equiv 1-p, \pmod{p^2},$$

since

$$\sum_{i=1}^{p} \frac{(-1)^{i-1}}{(p-i)\,!\,(i-1)\,!} = 0.$$

i.e.,

$$\frac{(-1)^{\frac{p(p+1)}{2}}}{\{1\,!\;2\,!\cdots(p-1)\,!\}^2} \equiv 1-p, \mod p^2$$

from which the required result follows.

It will be noticed that Theorem 8 gives a necessary and sufficient condition for p to be an odd prime.

Theorem 8 may also be proved as follows :—

$$1\,!\;2\,!\ldots.(p-1)\,! = (p-1)\,(p-2)^2\,(p-3)^3\ldots.2^{p-2}.\,1^{p-1}$$

Now $p-1 \equiv 1\,(p-1) \pmod{p^2}$

$$(p-2)^2 \equiv -2^2\,(p-1) \pmod{p^2}$$

$$(p-i)^i \equiv (-1)^{i-1}\,i^i\,(p-1) \pmod{p^2}$$

so that $(p-1)\,(p-2)^2\ldots.(p-i)^i \equiv (-1)^{\frac{(i-1)\,i}{2}} 1\cdot 2^2\cdot 3^3\ldots. \; i^i\,(p-1)^i \pmod{p^2}$,

$$\{(p-1)\,(p-2)^2\ldots.(p-i)^i\}^2 \equiv (1\cdot 2^2\cdot 3^3\ldots.i^i)^2\,(p-1)^{2i} \pmod{p^2}$$

Taking $i=\frac{p-1}{2}$ and multiplying both sides by

$$\left\{1^{p-1}\cdot 2^{p-2}\ldots.\left(\frac{p-1}{2}\right)^{\frac{p+1}{2}}\right\}^2$$

we get

$$[1\,!\;2\,!\ldots.(p-1)\,!]^2 \equiv \left(\frac{p-1}{2}\,!\right)^{2p}(p-1)^{p-1}, \pmod{p^2}.$$

If p be an odd prime

$$\left(\frac{p-1}{2}\,!\right)^2 + (-1)^{\frac{p-1}{2}} \equiv 0 \pmod{p},$$

so that $\left(\frac{p-1}{2}\,!\right)^{2p} \equiv \left[\left(\frac{p-1}{2}\,!\right)^2 + (-1)^{\frac{p-1}{2}} - (-1)^{\frac{p-1}{2}}\right]^p \equiv (-1)^{\frac{p+1}{2}} \pmod{p^2}$,

and $(p-1)^{p-1} \equiv \frac{-1}{p-1} \pmod{p^2}$,

whence we get Theorem 8.

From Theorem 8 we readily get

THEOREM 9. The necessary and sufficient condition that p be an odd prime of the form $1+x^2$ is $1\,!\;2\,!\ldots.(p-1)\,! \equiv \frac{\pm 1}{\sqrt{p-1}} \bmod p^2$.

If $a_i \equiv 0 \pmod{m}$ $(i=1, 2, \ldots. k)$ we have $\Pi\,(1-a_i) \equiv 1-\Sigma\,a_i + \Sigma\,a_i\,a_j$, $\pmod{m^3}$.

Therefore taking $a_i \equiv 1 + \frac{(-1)^{i-1}}{(p-i)!\,i!}$, we get, as for Theorem 8,

THEOREM 10. If p be an odd prime

$$\frac{(-1)^{\frac{p-1}{2}}}{\left\{1!\,2!\,3!\ldots\left(\frac{p-1}{2}\right)!\right\}^2} \equiv \frac{p-1}{2}\,\frac{(p-2)}{2} - \frac{(2p-2)!}{\{(p-1)!\}^4}, \pmod{p^3}.$$

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ON AN ASYMPTOTIC FORMULA IN PARTITIONS

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Received January 26, 1942

(Communicated by Dr. C. N. Srinivasiengar)

If $p_k(n)$ denote the number of partitions of n into exactly k summands, or what is the same thing, into summands the largest of which is k, then Erdös and Lehner[1] have recently proved the asymptotic formula:

$$p_k(n) \sim \frac{1}{k!}\binom{n-1}{k-1} \tag{1}$$

true for values of n for which

$$k = o(n^{\frac{1}{3}}).$$

In this note, I give an elementary proof of the above result.

2. Identically, we have

$$p_k(n) = p_k(n-k) + p_{k-1}(n-k) + p_{k-2}(n-k) + \cdots + p_1(n-k), \tag{2}$$

because if a partition of n in which the largest summand is k, be written down, and one element equal to k be deleted from it, we are left with a partition of $(n-k)$ in which the largest summand is either k or some smaller integer.

From (2) we immediately obtain the recurrence formula :

$$p_k(n) = p_k(n-k) + p_{k-1}(n-1); \tag{3}$$

whence

$$p_k(n) + p_k(n-1) + p_k(n-2) + \cdots + p_k(n-k+1) = \sum_{m=k}^{n} p_{k-1}(m-1) \tag{4}$$

3. We proceed to prove the

Theorem. For values of $j \geqslant 1$,

$$\frac{1}{j!}\binom{n-1}{j-1} \leqslant p_j(n) \leqslant \frac{1}{j!}\binom{n+c_j}{j-1}$$

where c_j is a function of j alone.

The theorem evidently holds for $j = 1$ with $c_j = 0$. Assuming it to be true for $j \leqslant k-1$, we notice that the right hand side of (4) is

$$\geqslant \frac{1}{(k-1)!}\sum_{m=k}^{n}\binom{m-2}{k-2} = \frac{1}{(k-1)!}\binom{n-1}{k-1}.$$

Of the k terms on the left hand side of (4), the greatest is $p_k(n)$, therefore

$$k.\, p_k(n) \geqslant \frac{1}{(k-1)!}\binom{n-1}{k-1}, \text{ i.e. } p_k(n) \geqslant \frac{1}{k!}\binom{n-1}{k-1}.$$

Again the right hand side of (4) is

$$\leqslant \frac{1}{(k-1)!}\sum_{m=k}^{n}\binom{m-1+c_{k-1}}{k-2}=\frac{1}{(k-1)!}\binom{n+c_{k-1}}{k-1},$$

while the left hand side of (4) is

$$\geqslant k\,p_k(n-k+1).$$

Hence $$p_k(n-k+1)\leqslant \frac{1}{k!}\binom{n+c_{k-1}}{k-1},$$

i.e., $$p_k(n)\leqslant \frac{1}{k!}\binom{n+c_k}{k-1},$$

where $c_k=c_{k-1}+(k-1)$, so that $c_k=\frac{1}{2}k(k-1)$.

The theorem is now readily proved by inductive reasoning.

4. From what has been proved above, we have

$$1\leqslant \frac{k!\,p_k(n)}{\binom{n-1}{k-1}}\leqslant \frac{n+c_k}{n-1}\cdot\frac{n+c_k-1}{n-2}\cdot\frac{n+c_k-2}{n-3}\cdots\frac{n+c_k-k+2}{n-k+1}. \tag{5}$$

The greatest factor on the right hand side of (5) is

$$\frac{n+c_k-k+2}{n-k+1}=\left\{1+\frac{k^2-k+2}{2(n-k+1)}\right\}.$$

Therefore the said product is

$$\leqslant \left\{1+\frac{k^2-k+2}{2(n-k+1)}\right\}^{k-1}.$$

Let $n=\dfrac{k^3}{q}$, where q is any finite quantity evidently $\leqslant k^2$, then

$$\left\{1+\frac{k^2-k+2}{2(n-k+1)}\right\}^{k-1}<\lim_{k\to\infty}\left(1+\frac{q}{2k}\right)^k=e^{q/2}.$$

Hence $$1\leqslant \frac{k!\,p_k(n)}{\binom{n-1}{k-1}}<e^{q/2},\ \text{where } q=\frac{k^3}{n}. \tag{6}$$

Thus when $k=o(n^{\frac{1}{3}})$, we must have

$$p_k(n)\sim\frac{1}{k!}\binom{n-1}{k-1}.$$

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EVAPORATION FROM WATER-DROPS AND WET SPHERICAL SURFACES*

By C. S. Karve, Ph.D.

Received March 3, 1942
(Communicated by Dr. K. R. Ramanathan)

1. *Introduction*

The problem of evaporation of water from cloud droplets, rain-drops, hailstones and snowflakes is one of great meteorological interest. The main factors which determine the evaporation are the size and shape of the condensed particles, their speed of movement relative to the surrounding atmosphere and the difference between the vapour densities at the surface of the particles and in the surrounding atmosphere. In the present paper, we shall only consider the problem of evaporation from spherical bodies.

2. *The Size and Speed of Particles which occur in the Atmosphere*

Water-drops occur in the atmosphere in sizes varying from an aggregation of a few molecules as in large ions ($r = 10^{-6}$ to 10^{-5} cm.) to droplets of cloud or fog (2 to 5×10^{-3} cm.), drizzle droplets ($r = 1$ to 5×10^{-2} cm. and rain-drops 5×10^{-2} cm. to 0·23 cm). The biggest rain-drops are about 0·45 cm. in diameter. Hailstones vary in size from that of rain-droplets to diameters of 10 cm. or more. The smallest rain-drops are spherical in shape; when the diameter increases to more than 0·1 cm. the drop becomes slightly flattened perpendicular to the direction of movement and the flattening increases with further increase of size, and ultimately when the diameter exceeds 0·45 cm. the drop breaks up into smaller droplets. Hailstones have varying shapes but well-formed ones tend to take up a conical form with a rounded base like a sector of a sphere.

The velocities with which the particles move in the atmosphere also differ considerably, the constant terminal velocity of a fog droplet being of the order of 1 cm. per second, while that of a hailstone may exceed the speed of an express train. The terminal speed of the biggest possible rain-drop is about 8 metres per second. Table I gives the radius r, the constant terminal velocity V and the Reynolds numbers $R = \frac{Vd}{\nu}$ of spherical or nearly spherical particles of water and ice. ν stands for the kinematic viscosity of air.

* Part of a Thesis approved for the degree of Ph.D. of the Bombay University.

TABLE I

Terminal velocities and corresponding Reynolds numbers of water-drops and spheres of specific gravities 1 *and* 0·915 *falling freely in air at sea-level pressure.* In the case of water-drops, the shape appreciably departs from the spherical as the size increases

Nature of falling body	Radius *r* in cm.	Velocity V in cm./sec.	R	Reference
Water-drops ..	0·001	1·2	·016	Lenard and Schmidt, quoted in Hann, *Lehrbuch der Meteorologie* (1926)
Do. ..	0·005	26	2	
Do. ..	0·01	78	10	
Do. ..	0·02	180	48	
Do. ..	0·05	430	290	
Do. ..	0·10	580	770	
Do. ..	0·15	690	1,380	
Do. ..	0·225	800	2,400	

Nature of falling body	Radius *r* in cm.	Velocity V in cm./sec.	R	Reference
Solid sphere of sp. gr. 1	0·05	400	270	N. Frössling
Do.	0·075	550	550	
Do.	0·10	680	905	
Do.	0·20	960	2,560	
Do.	0·30	1,190	4,760	
Solid sphere of sp. gr. 0·915	0·32	1,130	4,820	Adapted from Bilham and Relf[6]
Do.	0·63	1,550	13,000	
Do.	1·27	2,230	37,800	
Do. ..	1·91	2,740	70,000	
Do. ..	2·54	3,200	110,500	
Do. ..	3·17	3,570	151,000	
Do. ..	3·81	3,960	200,000	
Do. ..	4·44	4,360	258,000	

ν is assumed to be 0·150 cm.^{2}/sec.

3. *Review of Previous Measurements of Evaporation from Water-drops or Wet Porous Spheres*

There have been a number of previous measurements of evaporation from water-drops, but they have generally been on small drops. A few measurements of evaporation from moistened porous spheres of large size are also available.

H. Von dem Borne[1] investigated the evaporation of water from a wet porcelain ball of diameter 5·9 cm. at different wind speeds and for varying

values of relative humidity of the surrounding atmosphere. He found that the rate of evaporation could be expressed by the following formula:

$$\frac{E'}{\Delta\rho} = C\, f(V), \tag{1}$$

where E′ is the rate of evaporation from the sphere, $\Delta\rho$ is the difference between the vapour density at the surface of the moist sphere and in the surrounding atmosphere, C is a constant and f (V) is a function of velocity.

He found that in different ranges of wind velocity $\frac{E'}{\Delta\rho}$ had the following values. Here E′ is expressed in gm./min., $\Delta\rho$ in gm./metre^3 and V in metre/sec.

(*a*) V $<$ 2 metres/sec.

$$\frac{E'}{\Delta\rho} = 4{\cdot}3 \times 10^{-3}\,(1 + 1{\cdot}95\ V) \tag{2}$$

(*b*) V $>$ 3 metres/sec.

$$\frac{E'}{\Delta\rho} = 4{\cdot}3 \times 10^{-3}\,(1 + 2{\cdot}75\ \sqrt{V}). \tag{3}$$

If, instead of $\Delta\rho$, the difference of vapour pressure Δe is substituted (in mm. of mercury), (3) becomes

$$\frac{E'}{\Delta e} = 4{\cdot}55 \times 10^{-3}\,(1 - \alpha t)\,\frac{B}{750}\,(1 + 2{\cdot}75\ \sqrt{V}), \tag{4}$$

where B is the barometric pressure in millimetres of mercury and α is the coefficient of expansion of air at constant pressure.

K. Büttner[2] made measurements on a moist porous sphere of diameter 5 cm. and found that the rate of evaporation from this sphere in a wind stream could be expressed in the form

$$\frac{E}{\Delta e} = 12{\cdot}2 \times 10^{-5} \times V^{0{\cdot}52} \text{ gm./cm.}^2 \text{ min. (mm. Hg)}$$

Combining this result with theoretical considerations based on the analogy of evaporation from a wet surface to transfer of heat from a hot body, Büttner generalised the formula for different diameters of spheres and different wind velocities and expressed it in the form

$$\frac{E}{\Delta e} = \frac{0{\cdot}152}{d} \cdot \left\{ V d \times \frac{B_0}{B} \right\}^{0{\cdot}52} \text{gm./cm.}^2 \text{ min. (mm. Hg)}, \tag{5}$$

where E is the rate of evaporation in grammes per square centimetre per minute,

d is the diameter of the sphere in centimetres,

V is the speed of the air in metres/sec.,

B is the barometric pressure and B_0 is the standard barometric pressure.

Since the Reynolds number is Vd/ν, it follows that $\frac{E}{\Delta e}$ is approximately proportional to $R^{\frac{1}{2}}$.

H. G. Houghton[3] made measurements on drops ranging in diameter from 0·025 to 2·6 mm. at several temperatures and relative humidities and found that the theoretical relation deducible from the general diffusion equation, *viz.*,

$$\frac{dm}{dt} = 2\pi \, D d \, \Delta\rho \tag{6}$$

represents the results well.

In equation (6), $\frac{dm}{dt}$ is the rate of change of mass of a drop in gm./sec., D is the coefficient of diffusion of water vapour in air and d is the diameter of the drop.

Similar work on the evaporation from very small drops has been carried out by Takahasi and N. Frössling. Takahasi[4] worked on drops 0·2 to 1 mm. in radius with wind velocities ranging from 1·0 to 6·5 m./sec. He found the following relation for the rate of decrease of the radius of the drop with time.

$$\frac{dr^2}{dt} = -0{\cdot}45 \times 10^{-6} \, \Delta e \, (1 + 0{\cdot}173 \, V) \text{ cm.}^2\text{/sec.}, \tag{7}$$

where r is expressed in centimetres, V in metres per second and Δe in millimetres of mercury. Takahasi's method of determining the rate of evaporation was by measuring its diameter at successive times from its photographs.

Frössling[5] followed the same method as Takahasi and worked mainly in the range of diameters 0·1 to 0·9 mm. with wind velocities varying from 0·2 to 7 metres per second in a wind tunnel. He suspended the drops by a glass-fibre or a thermocouple. In addition to water-drops, he also studied drops of nitrobenzene and aniline. From his measurements, he verified the following approximate formula which he derived theoretically for Reynolds numbers below the critical range

$$\frac{dm}{dt} = 2\pi \, D d \, (1 + k\sqrt{R}) \, \Delta\rho, \tag{8}$$

where k is a constant characteristic of the evaporating substance (0·229 for water in air at 20° C.).

4. *Description of Present Experiments*

The experiments so far described were made either on small drops of water or on fairly large moist spheres. The measurements of Houghton, Takahasi and Frössling fall in the region of Reynolds numbers 0 to 600, while those of Borne and Büttner fall in the region 4,000 to 25,000. As the investigation of the region lying between Reynolds numbers 600 to 4,000 was considered to be of interest from theoretical and practical points of view, the following work was planned to measure the rates of evaporation from water-drops in the region of Reynolds numbers 200 to 10,000.

Considering the difficulty of working on small drops of water, the work was carried out on moistened porous spheres. After trying various substances such as pith, rubber, sponge, porous tiles, etc., it was finally found that blackboard chalk was a suitable substance both as regards porosity and strength. Therefore spheres of chalk of various diameters were prepared. For each series of measurements, a separate sphere of chalk was used. The arrangement of the apparatus for keeping the sphere moist and measuring the rate of evaporation is described below.

A glass tube ABCD (Fig. 1) bent twice at right angles at B and C was mounted with the limbs AB and CD vertical. The end D of the tube was

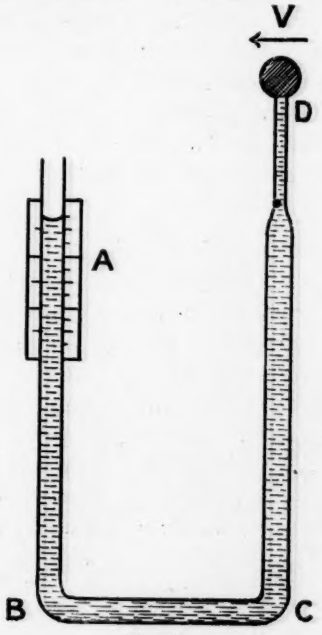

FIG. 1

drawn out into a thin capillary and the porous sphere of chalk was held in position at D by means of a thin horizontal needle. Enough water was poured into AB to come up to D in the capillary and feed the porous sphere. A scale was mounted just behind and in contact with AB to read the level of water in the tube. As the water from the chalk evaporated, the level of water in AB came down and the rate of evaporation could be determined from the rate of fall of water level in the tube. When working with different wind speeds and different spheres, the same fall of level between two fixed marks on tube (distant 0·5 cm. from each other) was used. The diameters of chalk spheres used were 0·30, 0·50, 0·75, 1·00, 1·50 and 2·00 cm.

Two different methods of varying the air speed were employed. In the first, the wind was produced by an electric fan and it was varied by varying the distance of the fan from the ball. The maximum wind velocity obtained with this arrangement was 3·5 metres per second. Higher wind speeds going up to 9 metres per second were obtained by means of an electric blower. The speeds could be varied by adjusting the resistance in the circuit of the motor and also by inserting sheets of wire-gauze in front of the blower. The wind speeds were measured at the place where the ball was mounted by means of a small hand anemometer made by Fuess or a vane anemometer made by Casella.

An attempt was made to measure the temperature of the evaporating sphere by means of a thin copper constant an thermo-couple, but as the thermo-junction was partly in contact with the wet sphere and partly in contact with air, the results were not considered satisfactory. The temperature was taken to be that of the wet bulb at the particular wind speed as calculated from the Pernter formulæ. The vapour pressure in the air at a distance from the sphere was calculated from the reading of an Assmamm psychrometer.

5. *Results*

(1) *Variation of E (rate of evaporation) with difference of vapour pressure between the moist surface and the air at a distance from the sphere, keeping V and* d *constant.*—The vapour pressure e of the air in the room was varied by working on different days and also by adding moisture to the air of the room as required from broad pans of warm water and mixing it up by fans. For each diameter of the sphere, the rate of evaporation was found to be proportional to $e_s - e$ or $\triangle e$ where e_s is the vapour pressure at the surface of the sphere, assumed to be given by the saturation vapour pressure at the wet bulb and e is the vapour pressure in the air of the room.

The results obtained with a sphere of diameter 2·0 cm. and wind speeds 0, 3, 6 and 9 metres per sec. are shown in Fig. 2 and are in agreement with Dalton's law. Similar results were obtained with other spheres.

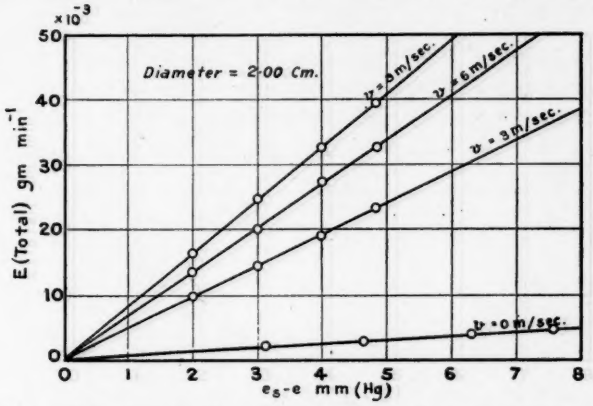

FIG. 2. Rate of evaporation against difference of vapour pressure

(2) *Variation of E with V when the diameter is kept constant.*—The results of the measurements on six spheres are plotted as curves in Fig. 3. For each sphere, as the speed of air increases, the rate of evaporation divided

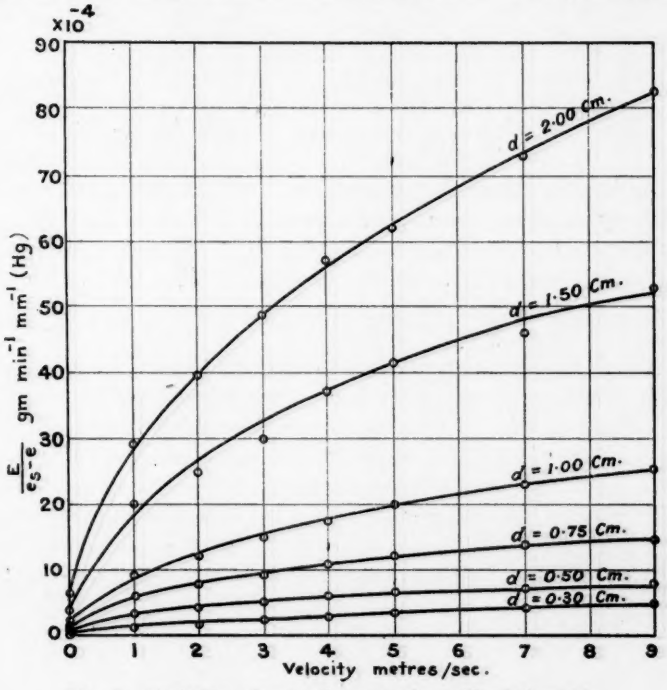

FIG. 3. Variation of rate of evaporation with wind speed

by the vapour pressure difference increases approximately in the form of a parabola, but the evaporation for zero wind does not come down to zero. By plotting log ($E/\Delta e$) against log V, it was seen that $E/\Delta e$ was very nearly proportional to $V^{\frac{1}{2}}$.

(3) *Variation of E with* d *when V is kept constant.*—If the wind were kept constant and expressed as a function of the diameter of the sphere, it was found that $E/\Delta e$ was approximately proportional to kd^n. n varied from 1·5 for no wind to 1·6 for a wind of speed 9 metres per second (see Fig. 4).

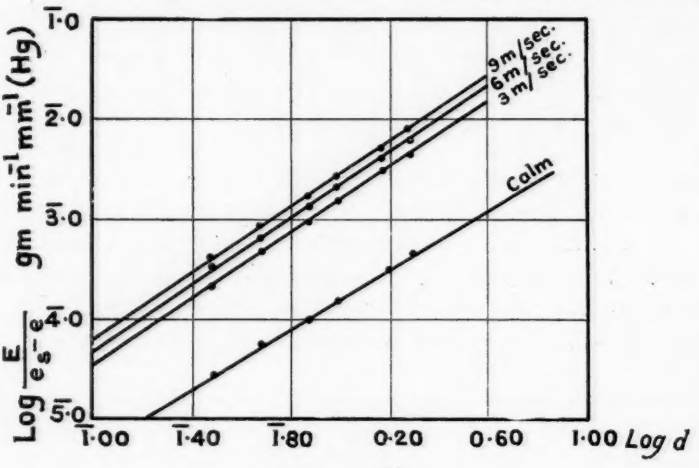

FIG. 4. Variation of $\frac{E}{e_s-e}$ with diameter

If, following Reynolds, momentum transfer and heat transfer from a solid body of given shape in a stream of fluid are considered similar, the simplest way to express the results for different wind speeds and different diameters of spheres would be through the Reynolds number. In Fig. 5 $\frac{E}{\Delta e \cdot d}$ is plotted against $\sqrt{R}$. The results obtained by V. d. Borne, Büttner, Houghton, Frössling and the author have all been plotted in the same figure, and except at very low Reynolds numbers, fall into a single curve. The gradually increasing slope of the curve with increasing values of R shows that a constant value of the exponent will not suit the results completely. At small values of R, the observed rate of evaporation is generally higher than that given by the simple diffusion formula and vary from author to author. In this region, greater reliance should be placed on the values obtained from

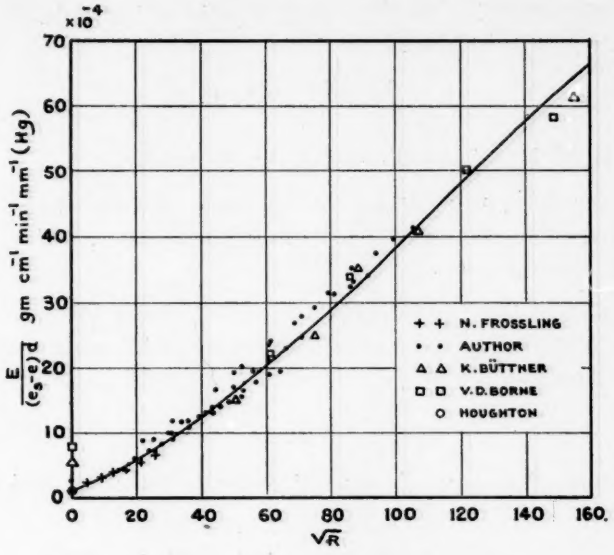

FIG. 5. Variation $\frac{E}{e_s - e}$ with Reynolds number

the experiments on small spheres, because with large spheres, the auto-convection due to the difference of temperature between the sphere and the surrounding air and the small air currents accidentally present even in a closed room will cause the effective value of R to be finite.

6. *Effect of Radiation on Evaporation*

In the above discussion, the effect of radiation between the evaporating sphere and the surrounding objects has not been considered. Owing to evaporation, the temperature of the sphere will tend to get down to that of the wet bulb, while owing to exchange of radiation with the surroundings, it will tend to become equal to that of the surrounding objects. When both processes are operating, the temperature of the sphere will be slightly greater than that of the wet bulb and the rate of evaporation increased. It is easy to calculate the rates of evaporation due to the two processes separately. The rate of absorption of radiant energy Q_R by unit area of a body is given by

$$Q_R = k\sigma\,(T_0^4 - T^4),$$

where k is the absorption coefficient of the surface of a body. σ is Stefan's constant $= 1{\cdot}37 \times 10^{-12}$ cal./cm.$^{-2}$/sec.$^{-1}$/deg.$^{-4}$, T is the absolute temperature of the body and T_0 the absolute temperature of the surrounding objects.

The rate of evaporation from a sphere of radius r due to the absorption of radiant energy will be given by

$$E_R = \frac{K\sigma\,(T_0^4 - T^4)}{L} \cdot 4\pi r^2$$

where L is the latent heat of evaporation of water.

For a wet sphere placed in a room, k may be taken as 1 and assuming, for example, $r = 1{\cdot}0$ cm., T = 20° C. and $T_0 = 28°$ C., $E_R = 1{\cdot}60 \times 10^{-3}$ gm./min.

In Table II below, are given the values of the rates of evaporation from spheres of different radii corresponding to a wet bulb temperature of 20° C. and air temperature of 28° C. at three different wind-speeds.

TABLE II

Comparison of amounts of evaporation due to convection and radiation

Wet bulb temperature = 20° C.

Temperature of surrounding objects and of air = 28° C.

Difference between vapour pressure at the surface of the wet bulb and at a distance = 4·1 mm. of mercury

Radius of sphere in cm.	E_R gm./min. (calc.)	E gm./min. (from curve)		
		No wind	V = 3 m./s.	V = 9 m./s.
1·00	$1{\cdot}6 \times 10^{-3}$	$4{\cdot}1 \times 10^{-3}$	$19{\cdot}7 \times 10^{-3}$	$3{\cdot}4 \times 10^{-2}$
0·50	$4{\cdot}0 \times 10^{-4}$	$1{\cdot}43 \times 10^{-3}$	$5{\cdot}8 \times 10^{-3}$	$1{\cdot}00 \times 10^{-2}$
0·25	$1{\cdot}0 \times 10^{-4}$	$4{\cdot}9 \times 10^{-4}$	$1{\cdot}9 \times 10^{-3}$	$3{\cdot}07 \times 10^{-3}$
0·15	$3{\cdot}6 \times 10^{-5}$	$2{\cdot}5 \times 10^{-4}$	$9{\cdot}4 \times 10^{-4}$	$1{\cdot}64 \times 10^{-3}$

It will be seen that the evaporation due to radiation is quite a considerable part of that due to convection, especially when there is no wind or the wind is weak. It was therefore thought desirable to calculate the rates of evaporation due to convection alone after allowing for the effects of radiation. The values of $E_{Total} - E_R$ instead of E (total) are used in Fig. 6 and shows that the general conclusions reached before are not modified in any essential respect. From the graph of log $(E_{Total} - E_R)$ against log d, the following slopes of the lines for different wind speeds were obtained.

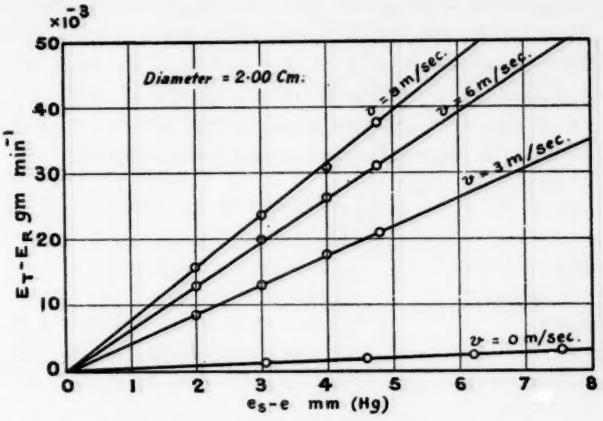

FIG. 6

Variation $E_T - E_R$ with vapour pressure difference

Wind speed m./s.	$\log \frac{(E_{Total} - E_R)}{\Delta e \times d}$
0	1·48
3	1·50
6	1·60
9	1·60
	Mean 1·55

This suggests that the value of the exponent n in the equation $\frac{E}{\Delta e \cdot d} = cR^n$ slightly increases with the Reynolds number and has an average value of 0·55.

My thanks are due to Dr. K. R. Ramanathan under whose direction the investigation was carried out and to the authorities of the Fergusson College in whose laboratories the measurements were made.

7. *Summary*

After a review of the sizes and velocities of free fall of water-drops and of solid spheres in the atmosphere and their appropriate "Reynolds" numbers, a summary of the previous work on evaporation from wet spherical surfaces is given. The paper then describes experiments made in the laboratory by the author on the evaporation from wet spheres of porous chalk in the range of Reynolds numbers 600 to 10,000. The

results of the present experiments and of the previous workers show that when $0 < R < 25{,}000$, the rate of evaporation from spheres of different sizes and in different wind speeds can be expressed as a function of R. When a suitable correction has been made for the effects of radiation, it is found that $E/(e_s - e)d$ can be expressed in the form cR^n where n increases from 0·48 to 0·60 when R increases from about 100 to 10,000.

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CHEMOTHERAPY OF BACTERIAL INFECTIONS

Part VII. Synthesis of Sulphanilamide Derivatives of the Pyrimidine Group

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(Communicated by Lt.-Col. S. S. Sokhey, M.A., M.D., I.M.S.)

In a previous publication,[1] one of us reported that the guanidine radical in sulphanilylguanidine does not undergo condensation with the β-ketonic esters, β-diketones and $\alpha : \beta$-unsaturated ketones as readily as guanidine or amidines. Further studies of these reactions showed that, in some cases, such a condensation could be effected in the presence of sodium ethoxide and this paper presents the results of these investigations.

Sulphanilylguanidine* condensed with ethyl acetoacetate in the presence of sodium ethoxide to yield a compound now identified to be 2-sulphanilamido-4-methylpyrimidone† (*vide infra*). This compound could also be prepared by condensing acetsulphanilylguanidine with ethyl acetoacetate and hydrolysing the corresponding acetsulphanilamido derivative obtained with about 4 N hydrochloric acid. Similarly, α- methyl, ethyl, *n*-butyl, *iso*-amyl and *n*-hexyl derivatives of ethyl acetoacetate condensed with sulphanilylguanidine yielding the corresponding 2-sulphanilamido-4-methyl-5-alkylpyrimidones in varying yields. These compounds as a class were soluble in alkali, very stable and exhibited the properties of the pyrimidones. In these condensations, only one product could be isolated in each case. Under these conditions, sulphanilylguanidine failed to condense with ethyl malonate and ethyl cyanoacetate.

For sulphanilylguanidine, two structures (I) and (II) are possible and it is very difficult from purely chemical methods to decide unequivocally

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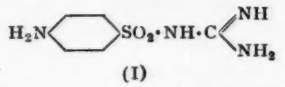
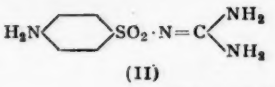
* Just before the foot-note in the paper of White *et al.*,[2] establishing the identity of sulphanilylguanidine with the product obtained by Buttle *et al.*[3] by the condensation of sulphanilamide with dicyandiamide, came to our notice, we also had come to the same conclusion not only by comparing the two compounds as such, but also the products obtained from them on condensation with ethyl acetoacetate.

† All the compounds described as pyrimidones in this paper can have the tautomeric 6-hydroxypyrimidine structure as well.

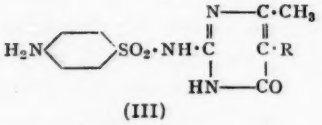
between the two.[4] Basing on the facts that the compound does not dissolve in alkali and does not condense with the β-ketonic esters as readily as the amidines, the structure (II) was suggested by one of us as more probable; but the limitations of this argument are obvious. For the coupound obtained by condensing sulphanilylguanidine with ethyl acetoacetate, which hereafter will for brevity be referred to by our serial number 76, four structures (III), (IV), (V) and (VI) (where R =H) are possible on the basis of the two formulæ (I) and (II) for sulphanily lguanidine. The formulæ (III)



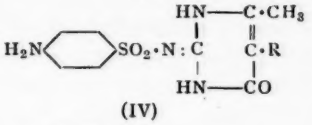
(I)



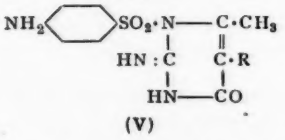
(II)



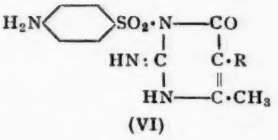
(III)



(IV)



(V)

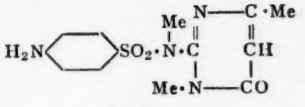


(VI)

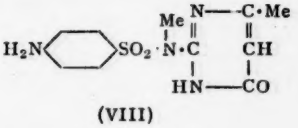
and (IV) can be considered to be tautomeric but there is no information as to the influence of the sulphanilyl group on the stabilising effect of the tautomeric forms. Since the compound 76 is soluble in alkali, the formula (VI) is to be rejected because a compound of this structure should be insoluble in alkali. A definite decision between the other possible formulæ (III), (IV) and (V) appeared to be possible by specific hydrolysis of the compound 76 at the imino or amino group attached to the carbon atom 2 of the pyrimidone ring for, by such a process, the compounds of formulæ (III) or (IV) should yield 4-methyluracil while that of formula (V) should furnish 3-sulphanilyl-4-methyluracil. But such a hydrolysis could not be effected. On boiling with about 30% sodium hydroxide for 6 hours, the compound 76 was recovered unchanged. While a little of it was decomposed by boiling with 4 N hydrochloric acid for about 2 hours, it underwent almost complete hydrolysis yielding sulphanilic acid and 2-amino-4-methyl-pyrimidone on refluxing with concentrated hydrochloric acid for about 6 hours. The isolation of 4-methyl-2-aminopyrimidone definitely proves that the compound 76 contains the 4-methylpyrimidone radical. The hydrolysis of the sulphanilamido derivatives with concentrated hydrochloric acid in many instances is known to cause fission at the sulphur-nitrogen linkage yielding the corresponding amine and sulphanilic acid[5,7]; but a compound of formula (V)

could be expected to be hydrolysed even with 4-6 N hydrochloric acid. For instance, it has been observed[6] that N-acetsulphanilylimidazole on boiling with 15% hydrochloric acid for half an hour yields imidazole and sulphanilic acid. So, we are of opinion that the results of the hydrolysis of the compound 76 suggests the rejection of the formula (V) for it. As a supplementary evidence it may be added that the pyrimidone derivative (76 Ac.) obtained by condensing acetsulphanilylguanidine with ethyl acetoacetate (which on hydrolysis yielded the compound 76) is insoluble in dilute hydrochloric acid indicating the absence of the free imino grouping.

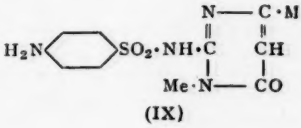
The other tangible difference between the three formulæ for the compound 76 is that in (III) there are two hydrogen atoms replaceable by sodium while in (IV) and (V) there is only one. When titrated with N/20 sodium hydroxide using phenolphthalein as the indicator, the compound 76 took about one molecular equivalent of alkali; but 2-sulphanilamido-4-methylpyrimidine and also 2-amino-4-methylpyrimidone under the same conditions took far less than one molecular equivalent of sodium hydroxide though both of these substances dissolved freely in alkali. Next, the compound of formula (III) should on methylation yield a dimethyl derivative insoluble in alkali and/or a monomethyl derivative soluble in alkali, while the compounds of formulæ (IV) and (V) should yield only a monomethyl derivative insoluble in alkali. The methylation of the compound 76 with dimethylsulphate in alkaline medium was therefore tried. Under a particular set of conditions, a compound insoluble in alkali was obtained which analysed correctly for a dimethyl derivative and this, from all the evidences taken together, can be represented as 2-sulphanilylmethylamido-1: 4-dimethylpyrimidone (VII). In addition, a product, which so far could not be obtained as a sharp melting one, was also isolated from the methylation products; this was soluble in alkali and appeared to be a mixture of the two possible isomeric monomethyl derivatives (VIII) and (IX) of the compound 76. These results therefore support the structure



(VII)



(VIII)

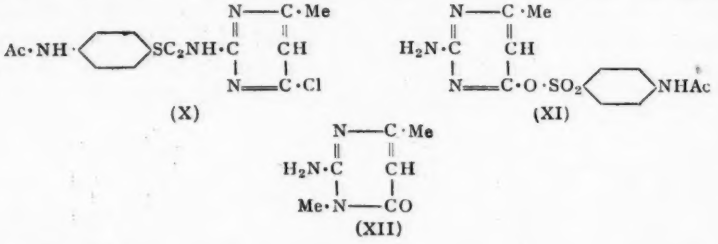


(IX)

(III, R = H) for the compound 76 and also (III, R = alkyl) for the others (compounds 101 to 104) obtained by condensing sulphanilyl guanidine with the α-alkyl acetoacetates.*

Attempts are being made to convert the N^4-acetyl derivative of the compounds 76 and 99 into the known 2-sulphanilamido-pyrimidines through the intermediate chloro-compound according to the standard procedure. On treating this N^4-acetyl derivative (76 Ac.) with phosphorous oxychloride according to the usual procedure, a chloro-compound not melting below 280° was obtained; this was soluble in alkali (indicating the presence of the sulphonamide grouping) and insoluble in all usual organic solvents. The analytical figures agreed well for the chloro-compound of structure (X) but its properties were quite unusual. Treatment of this with zinc dust and water did not lead to any definite results. Attempts to condense 2-amino-4-methyl-6-chloropyrimidine with acetsulphanilylchloride to prepare the chloro-compound of formula (X) were unsuccessful.

To obtain a compound of the structure (III, R = H) by the converse way, acetsulphanilylchloride was condensed with 2-amino-4-methylpyrimidone. While in the presence of pyridine only dark products were obtained, the condensation proceeded in good yields in alkaline (sodium bicarbonate) medium. The product obtained was soluble in dilute hydrochloric acid and insoluble in alkali. On boiling it with 2·5 N sodium hydroxide or 4 N hydrochloric acid for a few minutes, the starting material, 2-amino-4-methylpyrimidone was obtained in good yields. Thus, we assign the structure of the sulphonate (XI) to this compound in preference to the alternative structure of l-acetsulphanilyl-2-imino-4-methyldihydropyrimidone (acetyl derivative of VI). In support of the sulphonate structure,



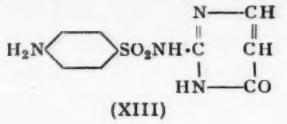
* *Note added in proof:* After this paper was sent for publication, Sprague, Kissinger and Lincoln (*J. Amer. Chem. Soc.*, 1941, 63, 3028) have described the preparation of a compound, 2-sulphanilamido-4-methyl-6-hydroxypyrimidine, m.p. 253·5–4°, by condensing acetsulphanilylchloride with 2-amino-4-methyl-6-ethoxypyrimidine and then hydrolysing the product obtained. The melting point of this agrees with that of our compound 76 and we are establishing the identity of the two by mixed melting points.

it has been found that 6-hydroxy-2-amino-pyridine[7] and also some aminophenols[8] yield only sulphonate derivatives with acetsulphanilylchloride. In some cases of the aminophenols, it has been observed that when sodium bicarbonate was used as the condensing agent the sulphonates are formed but with sodium acetate the sulphanilamido derivatives are obtained.[8] However, the condensation of 2-amino-4-methylpyrimidone with acetsulphanilylchloride did not proceed well in the presence of sodium acetate, the products obtained being acetsulphanilic acid and the starting amine. The sulphonate derivative (XI) could not successfully be condensed with another molecule of acetsulphanilylchloride. 2-Amino-4-methylpyrimidone was very readily methylated in alkaline medium with dimethylsulphate and the product obtained (XII) is probably identical with one of the compounds isolated by Majima[9] by condensing methylguanidine with ethyl acetoacetate. This methyl derivative also could not be condensed with acetsulphanilylchloride to obtain a product of formula (IX). It is of interest that while the 2-amino group in the pyrimidine derivatives is very reactive, the same grouping in the pyrimidone is comparatively inert.

Ethyl formylacetate condensed with sulphanilylguanidine in the presence of sodium ethoxide and the compound obtained can now, by analogy, be represented as 2-sulphanilamidopyrimidone (XIII). Formylacetone (hydroxymethlyeneacetone) was subjected to a similar condensation anticipating 2-sulphanilamido-4-methylpyrimidine ; but the product obtained in bad yield, even during crystallisation from water, decomposed yielding the starting sulphanilylguanidine. Hydroxymethylene methylbutylketone did not yield any appreciable amount of the condensation product with sulphanilylguanidine. These results are not unexpected since such a condensation even with guanidine proceeds only in bad yields.[10] Other conditions are being investigated.

Mesityloxide condensed with sulphanilylguanidine to yield, in different experiments but not simultaneously, two products, with m.p. 190–93° (compound 77*a*) and 135° (compound 77) respectively, and the conditions under which these are produced could not be defined exactly. These two compounds were insoluble in alkali and were of the same composition. It appears that they are dimorphic and this phenomena is being observed to an increasing extent in the compounds of the sulphanilamide group. Acetsulphanilylguanidine, on the other hand, condensed with mesityloxide in the presence of sodium ethoxide to yield a mixture of two products: (1) a compound, with m.p. 238–40°, insoluble in alkali and dilute hydrochloric acid, which on hydrolysis yielded the above described amino compound, melting at 190–93° (77*a*) and (2) a compound with m.p. 217–18°, soluble in

alkali and insoluble in dilute hydrochloric acid, which on hydrolysis yielded another amino compound having m.p. 230° (77*b*) and soluble in alkali. These two amino compounds (77*a*) and (77*b*) have been provisionally represented by the two possible structures (XIV) and (XV) respectively. The identity of the latter with the one obtained by condensing 2-amino·4 : 4 : 6-trimethyl dihydropyrimidine with acetsulphanilylchloride and subsequent hydrolysis[1] is being established.



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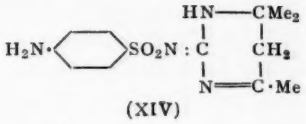
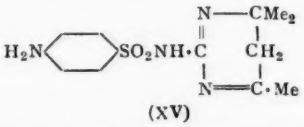


(XIV)



(XV)

Further work on the structures of these compounds is in progress. The results of condensing sulphanilylguanidine and acetsulphanilylguanidine with β-diketones will be presented in a separate communication.

The compounds described are being tested in experimental streptococcal, pneumococcal and *P. pestis* infections in mice and the results will be described in detail in due course. The compounds 76, 77*a* and 99 (XIII) were found to be devoid of therapeutic activity.

Experimental

2-*Sulphanilamidopyrimidone* (XIII) : *Compound* 99.—A mixture of ethylformate (14·8 g.) and ethylacetate (17·6 g.) was added gradually to powdered sodium (4·6 g.) suspended in dry ether (200 c.c.). The reaction mixture under ice cooling was stirred for about 3 hours and then allowed to stand overnight at the room temperature. The solid cake was separated from ether and mixed with sulphanilylguanidine (15·3 g.) and a solution of sodium ethoxide prepared by dissolving sodium (4·6 g.) in absolute ethyl alcohol (150 c.c.). The whole was heated under reflux for 2–3 hours, the alcohol distilled off, the residue shaken with water and filtered. The insoluble portion was the unreacted sulphanilylguanidine and the condensation product separated from the alkaline filtrate on acidification (yield, 50–60% of theory). On crystallisation from water, it separated in yellowish needles; m.p. 268–69°. (Found: N, 21·3; $C_{10}H_{10}N_4O_3S$ requires N, 21·1%.)

2-*Sulphanilamido*-4-*methyl*-5-*alkylpyrimidone* (III).—The compounds of this group were prepared by the following general procedure:

To a solution of sodium ethoxide prepared by dissolving sodium (about 1·5 molecular proportions) in absolute ethyl alcohol (about 10 times the quantity of sodium) was added successively about 1 molecular proportion each of sulphanilylguanidine and then ethyl acetoacetate or its α-alkyl derivative. The mixture was refluxed for 3–8 hours. The solid usually went into solution and then a crystalline product began to separate. Most of the alcohol was distilled off and on triturating the residue with water, the unchanged sulphanilylguanidine separated and was filtered off. The condensation product was isolated by just acidifying the alkaline filtrate with acetic acid. All the compounds crystallised well from dilute acetic acid or water. They were all soluble in alkali and dilute hydrochloric acid. The solubility in water was very moderate and as a class, the melting points were not very sharp and depended upon the rate of heating.

The condensation of acetsulphanilylguanidine with ethyl acetoactate or its alkyl derivative was carried out in the same way as described above. The acetsulphanilamido derivatives obtained were insoluble in dilute hydrochloric acid and soluble in dilute alkali. They were hydrolysed to the sulphanilamido derivatives by boiling with about 8–10 times the amount of 4 N hydrochloric acid till the solid went completely into solution (20–30 minutes) and then neutralising the clear filtered solution. By this process, the compounds obtained were identical with those prepared by the foregoing process.

The pyrimidone derivatives thus prepared are listed in the following table:

Serial No	R =	Yield %	M.P. °C.	Molecular Formula	% Nitrogen	
					Found	Required
			2-Sulphanilamido-4-methyl-5-(R)-pyrimidone (Formula III)			
76	Hydrogen	75	253-54	$C_{11}H_{12}N_4O_3S$	20·3	20·0
104	Methyl-	40	238–39	$C_{12}H_{14}N_4O_3S$	18·9	19·0
100	Ethyl-	70	208–09	$C_{13}H_{16}N_4O_3S$	18·2	18·2
101	*n*-Butyl-	30	121–22	$C_{15}H_{20}N_4O_3S$	16·2	16·7
102	*iso*-Amyl-	20	190–93	$C_{16}H_{22}N_4O_3S$	15·6	16·0
103	*n*-Hexyl-	60	108–10	$C_{17}H_{24}N_4O_3S$	15·2	15·4
			2-Acetsulphanilamido-4-methyl-5-(R)-pyrimidone			
76 Ac.	Hydrogen	30	273	$C_{13}H_{14}N_4O_4S$	17·5	17·4
102 Ac.	*iso*-Amyl-	20	228–29	$C_{18}H_{24}N_4O_4S$	14·0	14·3

Action of hydrochloric acid on 2-sulphanilamido-4-methylpyrimidone (*Compound* 76).—On boiling the product with 10 times the amount of about 4 N hydrochloric acid for 2 hours, a good deal of the starting material was

recovered unchanged. On boiling it with concentrated hydrochloric acid (37%) for 1/2 hour there was some hydrolysis. The following is a typical experiment wherein the hydrolysed products were isolated in good yields.

2 g. of the compound 76 was boiled with 20 c.c. hydrochloric acid (37%) for about 6 hours. The solution was evaporated to dryness whereby a mass of crystalline product separated. This was triturated with 25 c.c. of water whereby a portion of it went into solution. The portion remaining undissolved was crystallised from water and was identified to be sulphanilic acid. The solution was neutralised and the product obtained was crystallised from water and identified to be 2-amino-4-methylpyrimidone.

In none of the many experiments carried out could sulphanilamide be isolated.

Action of alkali on 2-*sulphanilamido*-4-*methylpyrimidone*.—On boiling the compound with ten times the amount of sodium hydroxide (30%) no change was perceptible and the starting substance was recovered unchanged on diluting the solution and acidifying it with acetic acid.

Methylation of 2-*sulphanilamido*-4-*methylpyrimidone*: *Isolation of* 2-*sulphanilylmethylamido*-1 : 4-*dimethylpyrimidone* (VII).—The following is one of the typical experiments wherein the methylated product was obtained with considerable ease. To 3 g. of the compound 76 dissolved in sodium hydroxide (10 c.c. of 2·5 N), acetone (25 c.c.) was added followed by dimethyl sulphate (4 c.c.). The mixture was refluxed for about 1 hour and allowed to stand for a day. The solvent was evaporated off, the residue triturated with a little alkali to make it distinctly alkaline and filtered. The solid was washed well with sodium hydroxide solution (about 5%) then with water and repeatedly crystallised from water, m.p. 160–65° (with previous shrinking). (Found: N, 18·3; $C_{13}H_{16}N_4O_3S$ requires N, 18·2%.) This is undoubtedly the dimethyl derivative (VII) of the compound 76. The alkaline mother liquor after the separation of this product was acidified with acetic acid whereby a gummy product separated which so far could not be obtained as a well-defined crystalline product. This product is being purified. It is definitely different from the starting compound 76 and is probably a mixture of the two monomethyl derivatives of formulæ (VIII) and (IX).

Action of phosphorousxychloride on 2-*acetsulphanilamido*-4-*methylpyrimidone*.—This acetyl compound (2 g.) was gently boiled with phosphorus oxychloride (6 c.c.) for about 2 hours, cooled and poured into ice. A solid product separated. It was filtered, dissolved in dilute sodium hydroxide solution and the filtered clear solution acidified whereby the chloro compound separated. It was insoluble in almost all organic solvents and

as such could not be recrystallised. It did not melt below 280°. [Found: N, 16·8; $C_{13}H_{13}N_4O_3SCl$ (formula X) requires N, 16·5%.]

On boiling with zinc dust and water, the product obtained also did not melt below 280° and was not free from chlorine.

2-*Amino*-1 : 4-*dimethylpyrimidone* (XII).—2-Amino-4-methylpyrimidone (5·0 g.) dissolved in sodium hydroxide (2·5 N, 25 c.c.) was treated with dimethylsulphate (6 c.c.) with good shaking. In a very short time a white crystalline precipitate separated. It was allowed to stand for about an hour, filtered and washed first with dilute sodium hydroxide and then with water. On crystallisation from water it separated in beautiful long needles; m.p. above 280°. (Found: N, 30·2; $C_6H_9N_3O$ requires N, 30·2%.)

[2′-*Amino*-4′-*methyl*-(6) *pyrimidonyl*] 4-*acetaminobenzenesulphonate* (XI): To a solution of 2-amino-4-methylpyrimidone (6·0 g.) in sodium hydroxide (2·5 N, 50 c.c.) was added sodium bicarbonate (13·0 g.) and then acetsulphanilylchloride (12 g.) with sufficient acetone to keep it in solution. The solution was stirred for about 3 hrs.; a white crystalline precipitate gradually separated. This was separated off and then another crop was obtained from the mother liquors on concentration. (Total yield, 8·2 g.) It separated from water in colourless needles and had m.p. 193–94°. (Found: N, 16·7; $C_{13}H_{14}N_4O_4S$ requires N, 17·4%.) This compound was insoluble in alkali but soluble in dilute hydrochloric acid. On boiling with 4 N hydrochloric acid or 2·5 N sodium hydroxide for about a few minutes, it furnished in very good yields the starting 2-amino-4-methylpyrimidone.

On condensing 2-amino-4-methylpyrimidone with two molecules of acetsulphanilylchloride the same condensation product was isolated. When sodium acetate was used as the condensing agent in the place of sodium bicarbonate, only the starting amine and acetsulphanilic acid could be isolated from the reaction mixture.

Condensation of acetsulphanilylguanidine with mesityloxide : Isolation of 2-*sulphanilylimido*-4 : 4 : 6-*trimethyl*-2 : 3 : 4 : 5-*tetrahydropyrimidine* (XIV) 2-*sulphanilamido*-4 : 4 : 6-*trimethyl*-4 : 5-*dihydropyrimidine* (XV).—To a solution of sodium (2·5 g.) in absolute ethyl alcohol (200 c.c.) was added finely powdered acetsulphanilylguanidine (25·6 g.) followed by mesityloxide (12·0 g.). The mixture was boiled under reflux for 3-5 hours. The red solution gradually lost its tint. After the refluxing was over, most of the solvent was distilled off and the residue triturated with water. A gummy product separated which on scratching solidified. This was filtered off (product A) and the alkaline filtrate acidified whereby another product (B) was obtained. The former formed the main bulk of the condensation product.

The product (A) was crystallised from dilute acetic acid or water; m.p. 241–42°. (Found: N,17·0; $C_{15}H_{20}N_4O_3S$ requires N, 16·7%.) This compound is insoluble in dilute hydrochloric acid and dilute alkali and is provisionally fixed to the N^4-acetyl derivative of (XIV). On hydrolysis with 4 N hydrochloric acid as usual, a compound crystallising in needles from water was obtained; m.p. 190–93°. (Found: N, 18·8; $C_{13}H_{18}N_4O_2S$ requires N, 19·0%.) This compound (77*a*) is soluble in dilute hydrochloric acid and insoluble in dilute sodium hydroxide and is provisionally represented as (XIV).

The product B, which was formed only in small quantities, crystallised from water acidified with acetic acid; m.p. 217-18°. This is soluble in dilute sodium hydroxide and insoluble in dilute hydrochloric acid. This is provisionally represented as the N^4-acetyl derivative of the compound of formula (XV). On hydrolysis with 4 N hydrochloric acid as usual, a product m.p. 228–30° was obtained. (Found: N, 19·6; $C_{13}H_{18}N_4O_2S$ requires N, 19·0%.) This compound (77*b*) is soluble in dilute hydrochloric acid and sodium hydroxide and is provisionally represented as (XV).

Condensation of sulphanilylguanidine with mesityl oxide.—This was carried out as described in the above case and 2 products were isolated in different experiments; but the exact conditions under which they are produced could not be defined. One of them (Compound 77) crystallised from alcohol in fine plates, m.p. 130–35°. (Found: N, 18·5; $C_{13}H_{18}N_4O_2S$ requires N, 19·0%.) Another product (77*a*) obtained was identical with the one described above, m.p. 190–93°. Both these compounds are insoluble in alkali. The melting points of these vary from sample to sample in a small range.

We express our grateful thanks to Lt.-Col. S. S. Sokhey, Director, Haffkine Institute, Parel, Bombay, for his keen interest in these investigations.

Summary

Sulphanilylguanidine condensed with ethyl acetoacetate and its α-alkyl derivatives to yield 2-sulphanilamido-4-methylpyrimidone and 2-sulphanilamido-4-methyl-5-alkylpyrimidones respectively. Experiments have been recorded which support these structures and a number of intermediate compounds are described. Ethyl formylacetate condensed with sulphanilylguanidine to furnish 2-sulphanilamidopyrimidone. Hydroxymethyleneacetone and hydroxymethylene ethylbutylketone failed to condense with sulphanilylguanidine to yield the corresponding pyrimidines in appreciable yields. Mesityl oxide, on the other hand, has yielded two products which are represented provisionally as the two possible pyrimidine derivatives (XIV) and (XV).

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CHEMOTHERAPY OF BACTERIAL INFECTIONS

Part VIII. Synthesis of Carboxylic Acid Derivatives of 2-Sulphanilamidothiazole

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(Communicated by Lt.-Col. S. S. Sokhey, M.A., M.D., I.M.S.)

In Part V of this series,[1] many alkyl derivatives of 2-sulphanilamidothiazole were described. In continuation of this, herein is reported the synthesis of some typical carboxylic acid derivatives with the acid grouping attached directly or through alkyl radicals to the thiazole ring in the positions 4 or 5. The synthesis of such acid derivatives has another object also. The exhaustive studies carried out hitherto with the various sulphanilamide derivatives have led to a novel application of these drugs for purposes wherein only their *in vitro* bacteriostatic and bactericidal effects are of prime importance. For one of such purposes are required solutions of these drugs in concentrations of the order of 1 to 30% at about 0° C. with the pH of the solution being as near as possible to 7·4. In the cases of 2-sulphanilamidopyridine and 2-sulphanilamidothiazole, such concentrations are possible only with their sodium salts and the pH of these solutions is about 10 to 11. We anticipate the sodium salts of the acid derivatives described here to satisfy our requirements.

The sulphanilamido derivatives herein reported were all synthesised by the usual method of condensing the 2-aminothiazole derivative with acetsulfanilylchloride and hydrolysing the resulting product. The hydrolysis was carried out in alcoholic hydrochloric acid or sodium hydroxide. When the conditions were more drastic, decarboxylation was also effected. For example, the hydrolysis of 2-acetsulphanilamido-4-methyl-5-carbethoxythiazole or 2-acetsulphanilamido-4-carbethoxymethylthiazole with about 5 N hydrochloric acid, yielded 2-sulphanilamido-4-methylthiazole. Similarly, 2-acetsulphanilamido-4-methyl-5-carbethoxymethylthiazole furnished 2-sulphanilamido-4: 5-dimethylthiazole. We are adopting this method to synthesise some alkyl and other derivatives of 2-sulphanilamidothiazole, the preparation of which by the usual methods are more involved.

The starting aminothiazole derivatives are all known excepting ethyl 2-aminothiazole-5-carboxylate and ethyl α-(2-aminothiazolyl)caproate. The

former was prepared by condensing thiourea with ethyl chloroformylacetate and the latter, which was not isolated, by the action of thiourea on the γ-bromination product of ethyl α-butylacetoacetate.

The compounds obtained are listed in the following table.

Serial No.	Name of Compound	M.P. °C.	Molecular Formula	% Nitrogen	
				Found	Required
96	2-Sulphanilamido-5-carbethoxythiazole	227–28	$C_{12}H_{13}N_3O_4S_2$	13·4	12·8
	2-Acetsulphanilamido-5-carbethoxythiazole	228–29	$C_{14}H_{15}N_3O_5S_2$	12·0	11·4
47	2-Sulphanilamido-4-methyl-5-carboxythiazole[a]	195	$C_{11}H_{11}N_3O_4S_2$	12·9	13·4
	2-Acetsulphanilamido-4-methyl-5-carbethoxythiazole[b]	154[g] (248)	$C_{15}H_{17}N_3O_5S_2$	11·4	11·0
48	2-Sulphanilamido-4-carboxymethylthiazole[c]	182	$C_{11}H_{11}N_3O_4S_2$	12·8	13·4
	2-Acetsulphanilamido-4-carbethoxymethylthiazole[d]	170–71	$C_{13}H_{17}N_3O_5S_2$	11·3	11·0
49	2-Sulphanilamido-4-methyl-5-carbethoxymethylthiazole	183–84	$C_{14}H_{17}N_3O_4S_2$	11·7	11·8
	2-Acetsulphanilamido-4-methyl-5-carbethoxymethylthiazole	203–04	$C_{16}H_{19}N_3O_5S_2$	10·6	10·6
97	α-(2-Sulphanilamido-(4)-thiazolyl) caproic acid	157–58	$C_{15}H_{19}N_4O_3S_2$	11·7	11·4
98	α-(2-Sulphanilamido-(4)-thiazolyl) *tert.*-butyric acid	174	$C_{13}H_{15}N_3O_4S_2$	11·9	12·2
	Ethyl α-(2-acetsulphanilamido-(4)-thiazolyl) *tert.*-butyrate	169–70	$C_{17}H_{21}N_3O_5S_2$	10·7	10·2
33	2-Sulphanilamido-4-methylthiazole[e]	236–37	$C_{10}H_{11}N_3O_2S_2$	15·0	15·1
81	2-Sulphanilamido-4 : 5-dimethylthiazole[f]	243–44	$C_{11}H_{13}N_3O_2S_2$	14·7	14·8

[a] Messrs. May and Baker's patent[2] records m.p. 190°. Jensen and Thorsteinsson[3] record m.p. 195°.

[b] Messrs. May and Baker's patent[2] records m.p. 249°. Jensen and Thorsteinsson[3] record m.p. 152·53°.

[c] Jensen and Thorsteinsson[3] record m.p. 185°.

[d] Jensen and Thorsteinsson[3] record m.p. 172·73°.

[e] Obtained by the hydrolysis of the acetyl derivative of compounds 47 and 48.

[f] Obtained by the hydrolysis of the acetyl derivative of compound 49.

[g] Melts at 154°, then solidifies and melts again at 248°.

These compounds are being tested in some experimental bacterial infections in mice and the results obtained will be reported in due course.

Experimental

Ethyl 2-aminothiazole-5-carboxylate.—To powdered sodium (4·6 gm.) suspended in dry ether (200 c.c.) was added gradually with stirring a mixture

of ethyl chloracetate (25 gm.) and ethyl formate (14·8 gm.). The reaction mixture was cooled with ice-water, the stirring continued for some hours and then allowed to stand overnight. Sufficient water (about 50 c.c.) was added to dissolve the sodium salt. The aqueous layer was separated, extracted with ether to remove any unchanged substance, neutralised and treated with thiourea (15·2 gm.). The mixture was allowed to stand overnight at the room temperature, then extracted with ether, and the acidic aqueous solution basified with ammonia whereby 2-amino-5-carbethoxythiazole separated. This was filtered and crystallised from water; m.p. 160–61°. (Found: N, 16·8; $C_6H_8N_2O_2S$ requires N, 16·3%.) Yield, 7 gm.

2-*Sulphanilamidothiazole Derivatives*.—These compounds were prepared according to the usual process. The condensation of the aminothiazole derivatives with acetsulphanilylchloride was carried out in the presence of pyridine. It was found to be advantageous to employ the esters themselves rather than the acid derivatives of the aminothiazoles. The hydrolysis of the acetsulphanilamido derivatives was carried by boiling with 6 times the amount of about 5 N hydrochloric acid with an equal volume of alcohol for one to one and a half hours. In many cases, this hydrolysed only the acetamino group, leaving the ester group intact which was then hydrolysed by boiling with alcoholic potash. If the hydrolysis was carried out with hydrochloric acid or 2·5 N sodium hydroxide and especially the boiling continued for about one hour, decarboxylation also took place furnishing the alkyl derivatives.

We express our grateful thanks to Lt.-Col. S. S. Sokhey, Director, Haffkine Institute, Parel, Bombay, for his kind interest in these investigations.

Summary

A number of carboxylic acid derivatives of 2-sulphanilamidothiazole with the acid grouping attached directly or through alkyl radicals to the thiazole ring at the positions 4 or 5, are described.

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A NOTE ON CERTAIN USEFUL COLOUR REACTIONS OF ANTHOXANTHINS AND RELATED COMPOUNDS

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That the reduction of flavones and flavonols yields bright red products was known even before Willstatter and other workers discovered that pyrylium salts of the anthocyanidin type are thereby formed. This reaction which is complex and gives rise to various products, has been very useful in establishing the relation between quercetin and cyanidin and has been freely employed for detecting the presence of flavones, flavonols and flavanones in plant materials. The reduction has been effected in different ways. In acid medium, usually alcoholic hydrochloric acid, the anthoxanthin has been reduced by the action of magnesium powder or magnesium in conjunction with mercury. The vigorous evolution of hydrogen is quickly followed by the appearance of bright red or allied shades of colour. When sodium amalgam is used instead, the alcoholic solution is finally acidified in order to produce the coloured pyrylium salt. In regard to the scope of the reduction in acid medium, Shinoda[1] examined a number of hydroxyflavones and flavonols and came to the conclusion that the presence or absence of hydroxyl groups in the side phenyl nucleus determined the nature of the final colour formed. When there were no hydroxyl groups in this phenyl nucleus yellow colours were obtained, whereas with increasing number of hydroxyl groups deeper red shades resulted. Later Asahina *et al.*[2] claimed that by employing acid and alkaline reducing agents it is possible to differentiate between flavones, flavonols and flavanones. According to them flavanones yielded red pyrylium salts by reduction by both the methods, *i.e.*, (1) magnesium and hydrochloric acid and (2) sodium amalgam. Flavonols respond to reduction in acid medium only and flavones yield definite colour reaction only with the alkaline reducing agent, sodium amalgam. A similar behaviour was noted with the isoflavones, genistein, pseudobaptigenin and osajin which like flavones undergo reduction with sodium amalgam, and not with magnesium and hydrochloric acid, to form red-coloured products (see Walter,[3] Wolfrom *et al.*[4, 5]).

In the course of our work we had occasion to examine a number of naturally occurring flavones and flavonols along with a number of synthetic

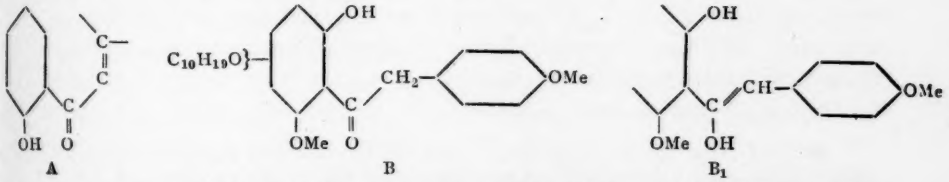
substances. Besides the hydroxylic compounds, completely methylated and sometimes partially methylated derivatives of these groups of compounds are found to occur in nature. Clear information of the behaviour of these methyl derivatives could not be obtained from the past literature. The clear-cut differences mentioned by Asahina *et al.* between flavonols and flavones, though valid in the simpler cases with a small number of hydroxyl groups, do not seem to hold good universally. For instance nobiletin[6] which is a flavone derivative gives a red colour when its alcoholic solution is treated with magnesium and hydrochloric acid. In regard to this reaction the results in general indicate that the pyrylium salt colours could range from golden yellow to deep red and purple, depending largely upon the number of hydroxyl groups present in the molecule. With less number of hydroxyl groups, say two, the colour is usually yellow or orange and with more heavily hydroxylated compounds it becomes deep red, brown red and purple. The methyl ethers seem to behave somewhat similar to the corresponding hydroxy compounds. The acetates, on the other hand, exhibit different properties; they give rise to practically no colour during the initial stages of the reduction and a colour develops only slowly, probably due to progressive hydrolysis by the alcoholic hydrochloric acid which gets hot during the course of the reaction. There does not seem to exist any sharp difference between flavones, flavanones and flavonols. It should, however, be noted that the first two groups due to the lack of a hydroxyl in the 3-position do not change into pseudo bases readily and hence do not require a high concentration of acid, whereas in carrying out the test for the flavonols sufficient amount of acid has to be added before the colour is seen. It may also be mentioned here that the addition of mercury does not seem to affect the course of the reduction with magnesium and hydrochloric acid to any appreciable extent.

With reference to reduction using sodium amalgam the same general considerations hold good. Though the difference pointed out by Asahina *et al.* between flavonols on the one hand and their methyl ethers and flavones on the other may be definite when pyrylium salts are prepared with larger quantities of materials, it is not quite dependable for qualitative tests using small quantities. In these tests even traces of products give colour and variations are introduced by the duration of the experiment, the concentrations of the solutions, etc. Using this method of reduction it is necessary to render the solution in the end strongly acid in order to obtain the colour. We have found that for this purpose sulphuric acid is more useful, since its concentration is high. Further, ordinary methylated spirit is preferable to anhydrous alcohol as solvent and reduction medium, since the latter solvent reacts only very slowly with the amalgam and hence the

reduction is too slow. From the typical cases mentioned later on, it is clear that flavonols also exhibit definite colour though compounds with no hydroxyl or with only a methoxyl in the 3-position form brighter red shades.

The boric acid test recently described by Wilson[7] is quite useful for detecting the presence of a 5-hydroxyl group in flavones and flavonols. Our results corroborate the structural features essential for a positive colour test as laid down by this author. A 5-methoxyl group serves equally well whereas an acetate group is unsuitable. In this connection it may be mentioned that similar conditions hold good even for the chalkones in which an *o*-hydroxyl or methoxyl gives rise to a positive colour. Incidentally it was noticed that when the simpler 3-hydroxyflavones without substitution in the 5-position are employed a marked blue fluorescence is generated, the solution remaining practically colourless. This suggests a possible method for the detection of small quantities of boric acid (compare Neelakantam and Row[8]) using these simple flavonols. The coming in of a 5-hydroxyl or methoxyl into the structure gives rise to deeply yellow solutions; no fluorescence could be detected in these cases.

From their work on osajin which is considered to be an iso-flavone derivative, Wolfrom *et al.* conclude that methylation of the hydroxyl in the system (A) leads to a negative boric acid test and that the compound (B) also gives a positive test probably due to enolisation as in (B_1). According to Wilson's statement a methoxyl group in place of a hydroxyl in the ortho position satisfies the requirements for a positive colour test. Our work confirms this as far as the flavones, flavonols and chalkones are concerned. The question therefore requires careful verification in regard to the isoflavones using more examples.



As regards the enol structure suggested by Wolfrom *et al.* being capable of giving the boric acid colour we note that resacetophenone which can form some enol of the required type does not give a positive reaction. A more comparable case is that of ω-phenylresacetophenone. When a pure sample of this is examined it does not give any colour in Wilson's boric acid test. Hence the claim of Wolfrom *et al.* that such compounds can

give a positive reaction by enolisation cannot be sustained. Obviously three requirements (1) a keto group, (2) an ortho hydroxyl or methoxyl and (3) an external double bond in conjugation with the C = O are essential for a positive boric acid reaction.

The results now obtained in the various tests are given below:—

I. *Reduction using magnesium and hydrochloric acid*

Simple flavones and flavonols.—7-Hydroxyflavone, 3-methoxy-7-hydroxyflavone, 3-hydroxy-7-methoxyflavone, 3:7-dihydroxyflavone and 2-methyl-3-methoxy-7-hydroxychromone—pale yellow; 3:7-dimethoxyflavone and 3-benzoyl-7-hydroxyflavone—golden yellow; 7-hydroxy-8-allylflavone and karanjin—deep orange yellow.

Naturally occurring flavones and flavonols and their derivatives.—Chrysin, luteolin and quercetagitrin—orange red; kæmpferol—feeble red; quercetin and patuletin—scarlet red; gossypetin, gossypitrin, herbacetin, populnetin and hibiscetin—brown red; quercetagetin—crimson; quercimeritrin, cannabiscetin, cannabiscitrin, hibiscitrin and isorhamnetin—red with pink tinge.

Pentamethylquercetin and pentamethylquercetagetin—orange red; hexamethylquercetagetin—deep crimson; 3, 7, 8, 3′, 4′-pentamethylgossypetin—brown; 7-acetyl-3, 5, 8, 3′, 4′-pentamethylgossypetin and hexamethylgossypetin—brown red.

Acetates of herbacetin, herbacitrin, gossypetin and patuletin—practically colourless for a few minutes during which the hydroxy compounds give a distinct and deep colour; slow development of the colour subsequently takes place due to hydrolysis.

Flavanone derivatives.—Naringin—bright pink; naringenin and hesperidin—reddish pink; butrin—brown pink; bu·in—deep bluish violet.

Some typical compounds belonging to other groups.—2, 6, 4′-trimethoxy-4-hydroxychalkone; 2:4-dihydroxy-4′-methoxychalkone, 7-hydroxycoumarin, 8-hydroxycoumarin, 5-hydroxy-4-methyl-coumarin and 5:7-dihydroxy-4-methylcoumarin—no colour.

II. *Reduction with sodium amalgam*

A few typical cases are given. 7-Hydroxyflavone and pentamethylquercetin—deep red; 3-methoxy-7-hydroxyflavone, 3-hydroxy-7-methoxyflavone and 3:7-dihydroxyflavone—orange-red; chrysin—brown red; quercetin—orange brown.

III. *Boric acid colour reaction*

The test was carried out in the way described by Wilson. But in the case of the methyl ethers a higher concentration of citric acid was found

to be advantageous. Though it was not necessary to dry the acetone marked "extra pure" available in the market, it was noted that the addition of a drop of water discharged the colour. Hence access of water should be avoided. The following naturally occurring hydroxyflavones and flavonols gave a positive reaction: chrysin, luteolin, kæmpferol, quercetin, quercetagetin, quercetagitrin, quercimeritrin, cannabiscetin, cannabiscitrin, herbacetin, gossypetin, gossypitrin, hibiscetin, hibiscitrin and patuletin.

Positive tests were also obtained with the following methyl ethers of compounds of the above class: Pentamethylquercetin, hexamethylgossypetin, pentamethylgossypetin-7-acetate and hexamethylquercetagetin.

Acetates of the following pigments gave negative results: Kæmpferol, herbacetin, herbacitrin, hibiscetin, quercetagetin, gossypetin and gossypitrin.

2, 4-dihydroxy-4′-methoxychalkone, 2, 4, 4′-trihydroxy-3′-methoxy-chalkone, 2, 4, 3′-trihydroxy-4′-methoxy-chalkone and 2, 6, 4′-trimethoxy-4-hydroxychalkone gave positive results.

Among compounds that gave negative results in this test were the following: naringin, hesperidin, butrin, 7-hydroxyflavone, 3-benzoyl-7-hydroxyflavone, 2-methyl-3-methoxy-7-hydroxychromone, 7-acetoxyflavone, 7-allyloxy-8-allylflavone, 2-methyl-3-acetyl-7-hydroxychromone, 3-benzoyl-7-hydroxycoumarin, 3-benzoyl-5 methyl-7-hydroxycoumarin, 3-acetyl-7-methoxycoumarin, 3-acetyl-5-methyl-7-hydroxycoumarin, 4, 8-dimethyl-7-acetoxycoumarin, salicylic acid, phenyl salicylate, resacetophenone ω-phenylresacetophenone and benzylidene-acetophenone.

3-Methoxy-7-hydroxyflavone, 3-hydroxy-7-methoxyflavone and 3: 7-dihydroxyflavone gave with boric and citric acids a colourless solution with blue fluorescence. The fluorescence of the first was rather feeble whereas the other two gave bright blue of about the same intensity, indicating that the hydroxyl in the 3-position is primarily responsible for the reaction. The fluorescence was easily visible in diffused daylight even with very small quantities of boric acid. Since the dihydroxyflavone is more easily prepared it has been employed for detailed tests. 0·5 c.c. of a 10% solution of anhydrous citric acid in acetone and 0·25 c.c. of a 0·1% solution of 3: 7-dihydroxyflavone in the same solvent were mixed in a tiny test tube (5/16″ diameter) and treated with 1 drop (0·02 c.c.) of 0·05% solution of boric acid in acetone, corresponding to 0·01 mg. of boric acid. There was appreciable fluorescence which could be detected with care. With two drops of boric acid solution (0·02 mg.) the observation of the fluorescence was much easier and with five drops (0·05 mg.) quite easy. One drop of a 0·5% solution of boric acid (0·1 mg.) gave under the

same conditions a brilliant blue fluorescence. It may be mentioned here that it was found desirable to carry out a blank test also at the same time with only the flavonol and citric acid using a similar test tube made of the same glass; this was because the glass had a small effect on the observation of the colour phenomenon. Carried out as described here the sensitiveness of the test for boric acid is of the order of 1 in 100,000.

A similar use could be suggested for the yellow colour formed with other compounds giving positive Wilson's test. A suitable case is pentamethylquercetin which forms colourless solutions in acetone containing citric acid. The yellow colour developed on the addition of boric acid solution could be easily noted. But the test is not so sensitive as with the fluorescence, only one part in 30,000 being capable of detection.

Summary

Employing a large number of natural and synthetic flavones, flavonols, flavanones and certain related compounds the scope of the following colour reactions has been examined: (1) reduction with magnesium and alcoholic hydrochloric acid, (2) reduction with sodium amalgam and alcohol and (3) Wilson's boric acid test using boric and citric acid mixture in acetone solution. For the first two reactions the nature of the colour depends in general upon the number of hydroxyl or methoxyl groups in the molecule. In qualitative reactions it is not easily possible to effect minor distinctions between flavones, flavonols and flavanones. The boric acid test is very specific for 5-hydroxy- and 5-methoxyflavones and flavonols and *o*-hydroxy- and methoxy chalkones. It is not given by flavanones and simple aromatic ketones which do not satisfy the specific conditions. A combination of these three colour reactions gives a great deal of useful information.

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A STUDY OF THE CHEMICAL COMPONENTS OF THE ROOTS OF *DECALEPIS HAMILTONII*

Part V. A Note on the Use of 4-*o*-Methylresorcylic Aldehyde as a Preservative

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In the preservation of canned and stored food, from the attack of bacterial and fungal organisms, certain preservatives like sulphur dioxide and benzoic acid were at one time freely employed. Since they have undesirable effects on health, laws have been enacted in various countries restricting their use. Recent trend has been in the direction of utilising natural preservatives which are not toxic to larger animals and which inhibit the growth of micro-organisms. Spices have been examined in this connection. Though they are not very good as such, volatile oils obtained from them have been found to be very satisfactory. Essential oil of mustard has proved itself to be a good preservative being even better than sulphur dioxide and benzoic acid. Oils of cinnamon, clove, thyme and bay leaves are also stated to be good.

It was noticed in the course of our work on the roots of *Decalepis Hamiltonii* and of *Hemidesmus indicus*,[1] that the air dried roots when kept for a long time, were uneffected by fungus and insects. Even the fresh roots were remarkably free from micro-organisms in the course of several days. It appeared that this was due to the presence of the sweet smelling volatile compound, 4-*o*-methylresorcylicaldehyde to the extent of 0·8% in the former and about 0·12% in the latter. It was therefore felt desirable to investigate the properties of this aldehyde as a preservative. The substance has a sweet and agreeable smell and a mild pungent and aromatic taste. It can be easily isolated by steam distillation of the powdered roots. A better yield can be obtained by extracting the material with alcohol and after distilling off the solvent, subjecting the residue to steam distillation. It can also be obtained in large quantities synthetically by the methylation of β-resorcylicaldehyde, using dimethyl sulphate and sodium hydroxide.[2]

Experiments were conducted to test roughly its toxicity to fish and bacteria. Small fresh-water fish known as *Haplochilus panchax* were employed for the former and B. Coli for the latter. It has been found that at a concentration of 0·021 per cent., a solution of it is toxic to fish and that they die within 4 minutes. The growth of B. Coli was arrested effectively in a

concentration of 0·041 per cent. for more than seven days. Two hydroxy-aldehydes isomeric with this, namely, vanillin and isovanillin were also studied with a view to understand the effcet of constitutional factors. Vanillin was toxic to fish at a strength of 0·029 per cent.; but they died only after 85 minutes. Iso-vanillin of the same concentration killed them in 2 hours. For bacteriostatic effect 0·231 per cent. solution of vanillin and 0·270 per cent. solution of iso-vanillin were required. Thus it is clear that the methyl ether of resorcylic aldehyde is far more effective than the other two. One disadvantage with it is that it is less soluble. However, in favour of its use as food preservative may be mentioned the fact that the *Decalepis* root is used largely in South India as a pickle and no untoward toxic effects on human beings have been noticed.

For purposes of characterisation of 4-*o*-methylresorcylicaldehyde the bromo-derivatives are useful (for their preparation see Rao *et al.*[3]). In the course of our work we have noticed that all the three products of bromination, (1) 5-bromo-aldehyde; (2) 3:5-dibromoaldehyde and (3) 2:4:6-tribromoresorcinol monomethyl ether could be obtained simultaneously by the following method. An ether solution of the aldehyde was treated with excess of bromine (in ether solution) at 0° and allowed to stand for 2 hours. The 5-bromoderivative (m.p. 120–121°) crystallised out by this time almost completely (yield 75%). It was filtered and the ether solution evaporated under reduced pressure. The residue was dissolved in alcohol and the solution allowed to concentrate. 3-5 dibromoderivative separated out in a small amount and could be purified by recrystallisation from aqueous alcohol. It melted at 98°. The mother liquor on treatment with water, gave a precipitate of impure 2:4:6-tribromoresorcinol monomethyl ether. Repeated recrystallisation from aqueous alcohol yielded the pure compound melting at 104-105° (yield 15%). It gave no colour with ferric chloride, did not exhibit any of the reactions of the aldehyde group and was found to be identical with a sample obtained from resorcinol monomethyl ether by treatment with excess of bromine in acetic acid solution. The mixed melting point was undepressed. (Found: C, 23·8; H, 1·5; and Br, 65·9. $C_7H_5O_2Br_3$ requires C, 23·3, H, 1·4 and Br, 68·4%.)

Similar results were obtained when acetic acid was used as solvent in the place of ether.

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CHEMICAL EXAMINATION OF INDIAN LICHENS

Part VII. Chemical Components of *Parmelia abessinica* (Rathipuvvu)

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Rathipuvvu (Telugu, meaning rock flower) is a lichen occurring abundantly in the rocky areas of the Western Andhra Districts of Bellary, Anantapur and Cuddapah in South India. It is used largely as a food material and some times is considered a delicacy. It also finds use in indigenous medicine. A sample of this was submitted to Kew for identification and was pronounced to be almost identical with *Parmelia abessinica* (Kremp).

A large number of species of *Parmelia* from different parts of the world have been studied by other workers. They seem to differ widely in chemical composition and even varietal differences are considerable. Since *Parmelia abessinica* has not so far been examined and since it is one of the most important of the Indian lichens, it has now been subjected to a detailed investigation using various solvents for extraction.

Careful cold percolation with petroleum ether removed most of the plastid pigments consisting of chlorophyll, carotene and xanthophyll. Subsequent extraction in a Soxhlet with the same solvent enabled the isolation of a crystalline compound which was identified as atranorin. In further succession ether, chloroform, acetone, alcohol and water were employed. The ether extract contained lecanoric acid; chloroform and alcohol extracted very small amount of amorphous material from which nothing definite could be isolated. Salazinic acid was the main component of the acetone extract and isolichenin was present in the aqueous extract. The same substances could be obtained by employing only ether, acetone and water in succession. Then the ether extract contained along with colouring matter, atranorin and lecanoric acid and they had to be separated carefully by using benzene and chloroform in which the former was soluble and the latter not. The other two extracts yielded salazinic acid and isolichenin. The yields of the various components were: Atranorin 1·1·%, Lecanoric acid 3·3%, Salazinic acid 0·1 to 0·5%, Isolichenin 3·4%. Employing samples obtained in different

years it was noticed that though the other components did not show marked change in yield, salazinic acid content varied appreciably.

In identifying the substances and studying their reactions certain new observations were made. (1) Methylation of lecanoric acid which was originally done by Fischer[1] using diazomethane can be equally well carried out using methyl iodide and potassium carbonate in acetone medium. Obviously in this and similar cases such as atranorin, chelation is not strong enough to interfere with the methylation of hydroxyl groups ortho to the carbonyl groups. (2) A pure sample of anhydrous salazinic acid is obtained by boiling the impure sample with pure acetone commercially available. Owing to the presence of impurties it dissolves fairly easily. From this solution the anhydrous acid crystallises out slowly. On the other hand if 80% acetone is employed for crystallisation the mono-hydrate is obtained.

Experimental

Samples of the lichen were obtained from Bellary, cleaned from adhering impurities, dried in the sun and stored. The results of proximate analysis expressed as percentage were as follows: moisture 13·9, reducing sugar 0·25, sucrose expressed as invert sugar 2·34, starch (lichenin) 27·39, nitrogen 0·98, ash 9·75. The ash contained phosphates, carbonates and silicates of iron, calcium and magnesium. The plastid pigments consisted of chlorophyll, carotene and xanthophyll.

Extraction with solvents

Petroleum ether: Atranorin.—The dry lichen powder (500 g.) was extracted in a modified Soxhlet apparatus with petroleum ether (b.p. 60–80°). The first few siphonings yielded dark green solutions due to the removal of the plastid pigments. This portion was discarded and the extraction continued. The colour of the extracts was only pale yellow. After about 20 hours the process was complete and no more was extracted. The yellow residue obtained on distilling the solvent was washed with small quantities of petroleum ether, ether and acetone in order to remove all colour. It was then crystallised once from xylene and then from benzene. Colourless prismatic crystals melting at 194–95° were obtained. The yield of the pure product was 5·5 g. 1·1%. [Found: C, 60·8; H, 5·2; OCH_3, 7·8; $C_{19}H_{18}O_8$ requires C, 60·9; H, 4·8; OCH_3 (ester) 8·3%.] The substance was easily soluble in hot chloroform and benzene and less soluble in other solvents. It was insoluble in aqueous sodium bicarbonate and only slowly in sodium carbonate to produce a yellow solution. It was readily soluble in potash with a deep yellow colour. With alcoholic ferric chloride it formed a wine red colour

and bleaching powder produced no change. The substance was therefore identified as atranorin. This was confirmed by the production of the characteristic chloroform containing compound by long boiling with this solvent and the preparation of the methyl ether by the action of methyl iodide and potassium carbonate, melting at 123° (Curd and Robertson[2]). [Found: C, 63·2; H, 6·0; OCH_3, 30·0; $C_{22}H_{24}O_8$ requires C, 63·4; H, 5·8; OCH_3, 29·8%.]

Ether: Lecanoric acid.—The lichen residue left after extraction with petroleum ether was dried and then extracted with ether for 24 hours. The first few extracts were coloured and were discarded. After distilling off the ether from the final extract a greenish solid was left. It was tested for any water-soluble portion and found to contain none. It was then dissolved in excess of cold acetone and diluted with an equal volume of water when most of the colouring matter separated out. It was quickly filtered and the filtrate diluted with a large excess of water and repeatedly extracted with ether. On distilling the ether a colourless solid was obtained which was easily soluble in alcohol, ether and acetone and insoluble in benzene and chloroform. It was finally purified by crystallisation from dilute acetone when colourless needles were obtained in an yield of 16·5 g. It melted with decomposition at 175°. (Found: C, 57·4; H, 4·9; loss on drying at 110°, 5·4. $C_{16}H_{14}O_7$, H_2O requires C, 57·2; H, 4·8; H_2O, 5·4%.) The substance was soluble in sodium bicarbonate, gave a violet red colour with alcoholic ferric chloride and bluish red with bleaching powder and reduced ammoniacal silver nitrate solution. It was identified as lecanoric acid and the identity was confirmed by fission of the depside link and identifying the products and by methylation using excess of methyl iodide and potassium carbonate, in anhydrous acetone medium. The acid in acetone solution was treated with excess of methyl iodide and potassium carbonate and the mixture was boiled for 60 hours. The solvent was then distilled off and water added in order to dissolve the potassium salts. The product was filtered and crystallised from aqueous acetone when it came out as colourless silky needles melting at 145–46°. It did not give any colour with alcoholic ferric chloride. [Found: C, 64·2; H, 6·1; OCH_3, 31·6; $C_{20}H_{22}O_7$ requires C, 64·1; H, 5·9; OCH_3 33·2%.] *Cf.* Fischer.[1]

Extraction with acetone

Salazinic acid.—The lichen residue left after ether extraction was again extracted with acetone in the same extractor for about 32 hours. The brown solution was distilled in order to remove the solvent and the residue boiled with a large excess of acetone. At this stage most of the solid dissolved

leaving behind a little coloured amorphous matter. The solution was quickly filtered, concentrated to some extent and allowed to stand. Colourless crystals (short needles) slowly separated out in good quantity. When heated, the substance was found to turn brown at about 260° to sinter at about 270° and swell and char at about 280°. [Found: C, 55·5; H, 3·0; $C_{18}H_{12}O_{10}$ requires C, 55·7; H, 3·1%.] It did not undergo any loss on drying at 120° *in vacuo* for 5 hours. It was insoluble in ether and chloroform and very sparingly soluble even in acetone. It could however be recrystallised from aqueous acetone (80%) when it came out as the monohydrate. The crystalline appearance was almost the same as the anhydrous sample except that the needles of the hydrate were longer and thinner and on heating it turned brown at 240°, sintered at 255° and swelled markedly and charred at about 260°. [Found: C, 53·2; H, 3·5; and loss on drying at 120°, 4·2; $C_{18}H_{12}O_{10}$, H_2O requires C, 53·2; H, 3·4; loss on drying 4·4%.] The substance was bitter to the taste, gave a brown red colour with alcoholic ferric chloride and formed a red solution with hot potassium carbonate yielding crystals of potassium salt having the characteristic crystal appearance of potassium salazinate (Asahina[3]). Its identity as salazinic acid was established by the preparation of the dianil by boiling the acid and aniline in 80% acetone solution. It was obtained as golden yellow prisms which were very sparingly soluble in most solvents and on heating turned orange yellow at about 240° and finally decomposed (charred) at about 280°. [Found: N, 5·4; $C_{30}H_{22}O_8N_2$ requires N, 5·2%.]

Extraction with water

Isolichenin.—The final lichen residue was heated with water in a boiling water-bath for 30 hours and filtered hot. On concentration over a water-bath an amorphous solid was obtained which gave the reactions of isolichenin. Its acetyl derivative crystallised from alcohol as needles melting at 115°. [Found: C, 49·7; H, 5·8; $C_6H_7O_5(COCH_3)_3$ requires C, 50·0; H, 5·6%.]

Summary

A complete examination of the lichen *Parmelia abessinica* is reported. Atranorin and lecanoric acid form the major lichen acids and salazinic acid the minor component. The presence of these three important lichen acids together is highly significant in regard to the biogenesis of these compounds.

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CHEMISTRY OF GOSSYPOL

Part II. The Anilino-Derivatives

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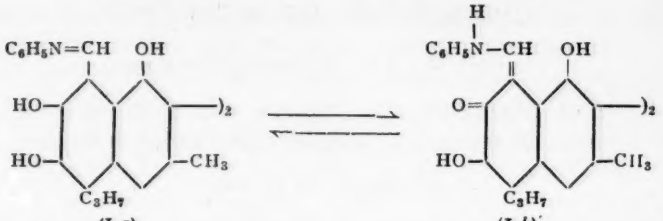
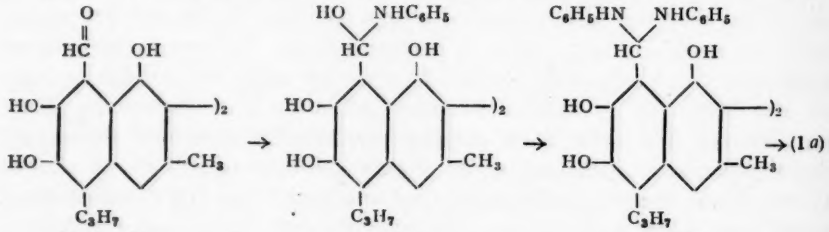
Gossypol combines with aniline very readily to form a highly characteristic deep yellow anilino-compound. Because of its sparing solubility, it has been used for purposes of estimation of gossypol and also for isolating it from cotton seeds.[5] Carruth[1] who was the first to prepare it noticed that the nitrogen analyses gave anomalous results. Though the substance which was dried by heating at 100° gave results agreeing with the formula G, $2C_6H_5NH_2$ (G = gossypol), the air-dried samples gave uniformly higher values for nitrogen and he represented the air-dried sample by the formula, $2G, 5C_6H_5NH_2$. Later workers, Clark[2] and Adams *et al.*[3] did not meet with this difficulty. They considered the compound to be dianilinogossypol arising as the result of condensation of two aniline molecules with two carbonyl groups present in gossypol with the elimination of 2 mols. of water. As a matter of fact, this was taken as an important confirmation for the existence of two such functional groups. The results of analysis for carbon, hydrogen and nitrogen and the determination of molecular weight were found by them to agree with this view.

In order to get further insight into the constitution of the anilino-compound, Adams *et al.* (*loc. cit.*) subjected it to acetylation and methylation. By the action of acetic anhydride and pyridine they reported the formation of hexaacetyldianilinogossypol which on pyrolysis yielded acetanilide as one of the products. From this they concluded that in the compound each of the nitrogen atoms was associated with a hydrogen atom which underwent substitution by an acetyl group during the above treatment. This was supported by their experiments on methylation using dimethyl sulphate and pyridine in chloroform solution. A red dimethyl product was isolated which was supposed to have methyl groups attached to the nitrogen atoms since they could not be removed by hydrogen iodide. Further the methylated compound could not be hydrolysed to gossypol under the conditions used for the hydrolysis of dianilinogossypol (sulphuric acid treatment). They also reported the isolation of another unintelligible compound designated dimethyldianilinooxogossypol under slightly different conditions of methylation. From these considerations they concluded that the dianilino-compound is not a simple Schiff's base but has constitution represented as below:



(I *a*) (I *b*)

In the course of the present investigation it has been observed that an air-dried sample of the anilino-compound, previously purified by crystallization from benzene, melts at 303° with decomposition, but at about 180° evolves considerable quantities of aniline which collects as a pale yellow liquid on the sides of the tube. Though the carbon and hydrogen values are very nearly the same as those required for the dianilino-compound, the nitrogen value is considerably high. This, however, agrees with the one required for a tetraanilino-compound. On heating at 110° for four hours or for much shorter period at 180°, it suffers a loss of weight of about 21% corresponding to the loss of two mols. of aniline. In other respects the oven-dried and air-dried samples behave very similarly. It may be mentioned that combustion values for carbon and hydrogen cannot differentiate between the two substances whereas the values required for nitrogen are capable of indicating the difference. (The dianilino-compound, $C_{42}H_{40}O_6N_2$ requires: C, 75·4; H, 6·0; N, 4·2 and the tetraanilino-compound, $C_{54}H_{54}O_6N_4$ requires : C, 75·9; H, 6·3; N, 6·6%.) It is thus obvious that gossypol forms a tetraanilino-compound which on drying undergoes change into the dianilino-compound with the evolution of aniline. In this respect it resembles aromatic aldehydes and the case is parallel to the findings of Hantzsch and Schwab[4] in regard to benzaldehyde and *p*-nitroaniline. The simple addition product (formula II) could be obtained by treating gossypol with exactly two molecular proportions of aniline. But it is not quite pure, being accompanied by small quantities of the dianilino-compound (I). The course of the reaction may be represented as below:



Gossypol (II) (III)

On heating dianilinogossypol at its melting point (303°) for sometime further evolution of aniline could be noticed. The residue is a dark uncrystallisable mass and nothing definite could be isolated from it.

In view of the ready decomposition of the anilino compounds with acetic anhydride[5] the findings of Adams *et al.*[3], who claimed to have obtained a diacetyl derivative of the dianil, seemed to be inexplicable. The reaction has, therefore, been repeated using acetic anhydride and pyridine. It is noticed that the main product when carefully purified is the yellow acetyl derivative of gossypol called by them " hexaacetyl-gossypol ". Thus the anils have behaved similar to gossypol itself obviously due to ready decomposition in the presence of acetic anhydride. It may be pointed out here that the melting point of the acetylation product mentioned by Adams *et al.* agrees with that of the ' yellow hexaacetyl-gossypol '. It is possible that the presence of nitrogen in their product was due to contamination with acetanilide, a large amount of which is produced particularly from the air-dried tetraanilino-compound. Again, methylation of the anilino compounds by the ordinary method using dimethyl sulphate and alkali yields the hexamethyl ether of gossypol itself, obviously due to the removal of the anilino groups. Consequently the conclusion of Adams and co-workers that the dianilino-compound has constitution I *b* does not seem to be supported.

In this paper the structure assigned by Adams *et al.* for gossypol has been tentatively adopted.

Experimental

Preparation of Tetraanilinogossypol (III).—Gossypol (1 g.) was treated with aniline (10 c.c.) and the mixture was just heated to boiling, whereby a clear solution was obtained. On allowing it to cool an orange-yellow crystalline precipitate was obtained. It was filtered and washed first with alcohol and then with ether. It was finally recrystallised from hot benzene when it was obtained as glistening yellow rectangular plates. After air-drying at the ordinary temperature for over a week, it melted with decomposition at 303°. It was however noticed that a small quantity of a liquid (aniline) condensed on the sides of the melting point tube at about 180°. (Found: C, 76·0; H, 6·3; N, 6·8; $C_{54}H_{54}O_6N_4$ requires: C, 75·9; H., 6·3; N, 6·6%.) The compound could also be prepared by the addition of excess of aniline to a solution of gossypol in ether. It was sparingly soluble in most of the organic solvents and it could be best crystallised from boiling aniline or benzene.

Dianilinogossypol.—The tetraanilinogossypol (1 g.) was heated at 100° to 110° in an air oven for four hours till there was no further loss in weight. This loss amounted to the removal of 2 mols. of aniline. The product was crystallised from boiling benzene and was obtained as bright yellow rectangular plates (Found: C, 75·3; H, 6·1; N, 4·3; $C_{42}H_{40}O_6N_2$ requires : C, 75·4; H, 6·0; N, 4·2%.) On heating in a capillary tube it did not evolve any aniline at about 180° but melted with decomposition at 303°. In its solubility and in other reactions it closely resembled the tetranilino-compound. Even the mixed melting point was undepressed. If the decomposition was carried out in a small distillation flask connected to a pump through a condenser and the heating was done at 180° using an oil bath, it was found to be over within an hour and in the distillate aniline could be identified.

Formation of the compound II.—Gossypol (0·5 g.) dissolved in dry ether (10 c.c.) was treated with a solution of aniline (0·2 g.) in the same solvent. On stirring, a crystalline precipitate rapidly formed. After about an hour it was filtered, washed with ether and subsequently with alcohol and allowed to dry at the room temperature. It was a yellow crystalline substance (ill-defined plates) melting with decomposition at 303°. (Found: C, 72·9, H 6·1; $C_{42}H_{44}O_8N_2$ requires: C, 71·6, H, 6·3%.) Compound II seems to be therefore mixed with some amount of the di-anilino compound arising as the result of removal of water.

Action of heat on the dianil.—A sample of pure dianilinogossypol was taken into a short test tube provided with a side neck which was connected to a pump through a receiver. It was gradually heated in a metal bath to a temperature of 300° in the course of about an hour. A dark amorphous mass was formed in the test tube and the distillate was identified to be aniline. The residue consisted mostly of dark tarry matter from which a very small quantity of an yellow substance could be extracted with alcohol. The latter gave no test for nitrogen.

Action of acetic anhydride.—The solution of the tretraanilino compound (0·5 g.) in pyridine (10 c.c.) was treated with acetic anhydride (5 c.c.) and heated on a steam-bath for 30 minutes following exactly the method of Adams *et al.* (*loc. cit.*). About 10 c.c. of acetic acid was then added and the mixture poured into water. The solid product was crystallised from methyl alcohol. It was found to be a bright yellow crystalline solid melting at 185° with decomposition and exhibiting most of the properties mentioned by the above authors. It, however, contained no nitrogen and hence could not be a derivative of the anilino-compound. It was also different from

gossypol-acetic acid since it did not give any colour reaction with ferric or stannic chlorides, and was unaffected by cold dilute alkali. It was however, found to be identical with yellow hexaacetyl-gossypol in all respects and mixed melting point with it was undepressed.

The same product was obtained when dianilino-gossypol was employed.

Methylation of the Anilino compound.—The tetraanilino-compound (0·5 g.) was dissolved in 20% alcoholic alkali (5 c.c.) and the solution treated with dimethyl sulphate (3 c.c.) with vigorous shaking and keeping the contents slightly alkaline. After decomposing the excess of dimethyl sulphate by heating the solution for 1 hour, on a water-bath, water was added and the solid precipitate was filtered and purified by crystallisation from acetone-methyl alcohol mixture. It was a pale brown crystalline substance melting at 130° and containing no nitrogen. (Found: OCH_3, 31·0% ; $C_{30}H_{24}O_2$, $(OCH_3)_6$ requires OCH_3, 30·9%.) The same result was obtained when dianilinogossypol was used.

Summary

With excess of aniline, gossypol forms tetraanilino-gossypol which decomposes on heating for a long time at 110° or for a short period at 180°, the products being aniline and dianilinogossypol. The two anilino compounds resemble closely except for the fact that the tetraanilino-compound contains more nitrogen and evolves aniline long before its final decomposition point is reached. Acetylation and methylation yield only gossypol derivatives, aniline being removed; acetyl and methyl derivatives of the anilino compounds could not be obtained.

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CHEMISTRY OF GOSSYPOL

Part III. Methylation

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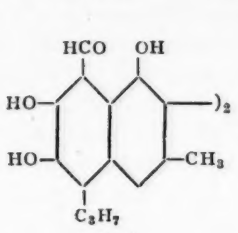
Gossypol is highly reactive and unless the hydroxyl groups are protected, no definite degradation products could be obtained. In the elucidation of the constitution of gossypol, therefore, methylation is an operation of great importance. Adams and co-workers were the first to use it and consequently they were successful in obtaining a large number of degradation products through which much light was thrown on the constitution of the parent compound. However, a study of their work indicates the existence of a number of discrepancies. During the course of their voluminous work several samples of hexamethyl ether of gossypol, differing widely in their appearance and melting point were obtained. In all their experiments, they used dimethyl sulphate and carried out the methylation under various conditions. During the earlier part of the work, by the methylation of gossypol they[1] obtained a red hexamethyl ether melting at 160° and a colourless variety melting at 237°. These were recorded to be interconvertible and their existence was attributed to easy tautomerism. Later, starting from dimethyl gossypol they[2] obtained a hexamethyl ether which melted at different temperatures depending upon the solvent employed for crystallisation. When methyl alcohol was employed, the melting point was 211° whereas with a mixture of methyl alcohol and acetone it was 223° and with ligroin 173°. At a later stage[2] gossypol-acetic acid was used as the starting material. When the methylation of this compound was carried out at 10–15° the resulting sample of the hexamethyl ether of gossypol melted at 240° whether crystallised from acetone-methyl alcohol mixture or ligroin; when the temperature employed was 20–25° the melting point of the product was 225°. A third method[3] in which the tetramethyl ether was an intermediate stage produced a hexamethyl compound melting at 175°. It is therefore clear that marked differences in the nature of the product were brought about by differences in experimental technique and the solvent employed for crystallisation. However, all samples were found to have the same chemical properties and these authors felt that 'their exact character is not very significant'. Obviously, all these differences could not be explained as due to isomerism. As already

explained in our previous publication[4] the existence of different forms of gossypol itself does not seem to be so definite. Throughout their work it is noteworthy that Adams *et al.* made no determination of methoxyl value for the reason that they felt that it was unreliable. They found that even gossypol gave considerably high methoxyl value though it contained no methoxyl groups. Consequently they relied entirely on the determination of carbon and hydrogen for controlling the purity of the compounds. This does not seem to be satisfactory since marked difference in the percentages of carbon and hydrogen do not occur with variation in the methoxyl content, as for example the values of carbon and hydrogen for the pentamethyl ether are 71·4 and 6·8% whereas for the hexamethyl ether, the values are 71·8 and 7·0%. Therefore, the possibility of incomplete methylation and other differences in composition as the causes of the above discrepancies are not excluded. Efforts have therefore been made now to prepare the hexamethyl ether in a pure condition with definite and constant properties.

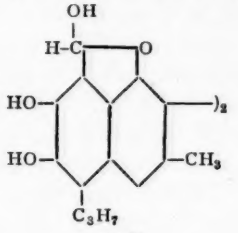
The provisional structure (I *a*) given by Adams *et al.* for gossypol contains ortho-hydroxy-aldehyde groups. It was first expected that these may offer difficulties in methylation due to chelation. The substance is also unstable in the presence of alkali. For similar cases met with among flavones and flavonols methylation of the acetyl derivatives using dimethyl sulphate in the presence of acetone and potash has been found in these laboratories[5] to be very successful. The products were completely methylated derivatives. Using gossypol hexaacetate for our present purpose a pure sample of the hexamethyl ether was obtained. It was very pale yellow in colour and melted at 130°. Its methoxyl value was quite normal as also the values for carbon and hydrogen. It has already been mentioned in our earlier publication[4] that our sample of gossypol gave no methoxyl value.

With a view to find out how far hindrance existed for complete methylation, gentler methods of methylating gossypol were adopted. Methylation using diazomethane and a methyl alcoholic solution of gossypol as well as methylation employing methyl iodide and potassium carbonate in anhydrous acetone medium gave the same hexamethyl ether easily. No partially methylated compounds could be obtained. Thus there seems to be no resistance to methylation. Further it was noted that by employing a mixture of gossypol and dimethyl sulphate in methyl alcoholic solution and adding potassium hydroxide solution a similar result is obtained. Thus complete methylation of gossypol takes place with ease yielding the same hexamethyl ether. The lower melting point of the ether as compared with gossypol is also according to expectations. That this is not due to hydration is clear from the fact that the sample is anyhydrous.

The ready methylation of gossypol may be satisfactorily explained by the formula I *b* of Adams *et al.* in which no free aldehyde groups exist. But the methyl ethers of such structures should undergo ready hydrolysis with dilute acids simulating the behaviour of glycosides. No such change was found to take place. The hexamethyl ether was quite stable in boiling dilute sulphuric acid. Consequently the aldehydic form is not excluded and the absence of the effect of chelation may be due to steric factors.



(I *a*)



(I *b*)

Experimental

Preparation of hexamethyl ether from hexaacetate.—Gossypol hexaacetate (white) melting at 276° was employed. This substance (1 g.) was dissolved in acetone (20 c.c.) and treated with dimethyl sulphate and 20% sodium hydroxide solution (5 c.c. each). After shaking vigorously for some time more of dimethyl sulphate (3 c.c.) and alkali (5 c.c.) were added alternately in small quantities. Vigorous shaking was given after each addition and the solution was kept alkaline. The contents were allowed to stand overnight and then boiled under reflux for one hour. When the solvent was subsequently distilled off, a pale brown solid separated. It was collected and crystallised from dilute acetone.

The methyl ether obtained as given above appeared in bulk as a pale brown crystalline solid; under the microscope, it had the form of light yellow rectangular plates. It melted down to a liquid at 130° with sintering a few degrees earlier. It did not dissolve in aqueous alkali but was readily soluble in alcohol, acetone and other common organic solvents. Alcoholic solution gave no colour with ferric or stannic chlorides. Concentrated sulphuric acid gave light orange colour in contrast to the scarlet red colour obtained with gossypol. (Found: C, 72·0; H, 7·1; OCH_3, 30·5; $C_{30}H_{24}O_2(OCH_3)_6$ requires C, 71·8; H, 7·0; OCH_3, 30·9%. $C_{30}H_{26}O_4(OCH_3)_4$ requires C, 71·1; H, 6·6; OCH_3, 21·6%.)

Direct Methylation of Gossypol

(*a*) *With diazomethane.*—Gossypol (1 g.) was dissolved in absolute methyl alcohol (30 c.c.) and the clear solution was treated with a large

excess of diazomethane (obtained from 10 g. of nitroso-methyl urea) in ether solution. The reagent was added in two lots on two successive days. After adding the first half in small quantities attended with shaking, the mixture was allowed to stand for 24 hours and as much ether as possible distilled off using a hot water-bath. After cooling, the second half of the reagent was slowly added. After standing overnight the solvents, ether and alcohol, were completely distilled off. On adding water to the residue a yellow crystalline solid separated and it was purified by crystallisation from dilute acetone. The crystal structure, melting point and other properties were the same as those possessed by the hexamethyl ether obtained from the acetate. The mixed melting point was unchanged. (Found: C, 71·9; H, 7·0; OCH_3, 30·5; $C_{30}H_{24}O_2$ $(OCH_3)_6$ requires C, 71·8; H, 7·0; OCH_3, 30·9%.)

(*b*) *With methyl iodide.*—A solution of gossypol (2 g.) in anhydrous acetone (50 c.c.) was treated with anhydrous potass. carbonate (10 g.) and methyl iodide (15 c.c.) was added slowly in small quantities at a time. The contents were kept gently boiling under reflux for 48 hours. The solvent was then distilled off and the residue treated with water in order to dissolve the carbonate. The insoluble yellow solid was filtered, washed with water and finally crystallised from acetone-methyl alcohol mixture. This sample of the hexamethyl ether had also the same melting point and other properties as already described. The mixed melting point with previous samples was undepressed. [Found: C, 71·9; H, 7·1; OCH_3, 30·6; $C_{30}H_{24}O_2$ $(OCH_3)_6$ requires C, 71·8; H, 7·0; OCH_3, 30·9%.]

(*c*) *With dimethyl sulphate.*—Gossypol (1 g.) was treated with a mixture of absolute methyl alcohol (5 c.c.) and freshly distilled dimethyl sulphate (5 c.c.) and warmed on a steam-bath. When a clear solution was obtained 10% methyl alcoholic potash (3·5 c.c.) was added in quantities of half c.c. each time and vigorously shaken. The reaction flask was then stoppered and allowed to stand for 24 hours with occasional shaking. The excess of dimethyl sulphate was decomposed by adding more alkali and warming. On adding excess of water a light brown flocculent precipitate was formed. It was filtered and crystallised from dilute acetone. Though a little brown colour persisted even after repeated crystallisations the substance was otherwise identical with samples of hexamethyl ether obtained by the methods given above. (Found: C, 72·0; H, 7·1; OCH_3, 30·4; $C_{30}H_{24}O_2$ $(OCH_3)_6$ requires C, 71·8; H, 7·0; OCH_3, 30·9%.)

All the samples of the hexamethyl ether melted without decomposition and gave satisfactory methoxyl values. Further repeated recrystallisations brought about no change in the melting point or analytical values.

The methods which did not employ aqueous alkali (diazomethane or methyl iodide and potassium carbonate) yielded samples which had a pale yellow colour whereas those in which caustic alkali had to be used left a pale brown colour with the samples and it could not be removed completely by repeated crystallisations. Though the hexamethyl ether exhibited sintering below 130° it did not contain any solvent of crystallisation since it lost no weight on drying *in vacuo* and gave satisfactory and consistent analytical values.

Gossypol hexamethyl ether (0·5 g.) was dissolved in dilute alcohol (20 c.c.) and enough of concentrated sulphuric acid (0·8 c.c.) added so as to bring its concentration to about 7%. The mixture was then boiled under reflux for 2 hours. When the alcohol was distilled off a precipitate was formed. When filtered and crystallised from dilute acetone, it was found to be the original hexamethyl ether recovered unchanged.

The experiment was repeated using hydrochloric acid and even in this case no demethylation took place.

However, by boiling with glacial acetic acid containing concentrated sulphuric acid, partial demethylation to gossypol dimethyl ether could be effected (compare Adams, *et al.*[2]).

Summary

The methods adopted by Adams *et al.* for the methylation of gossypol do not seem to produce a uniform product of the hexamethyl ether having constant properties. The following methods have now been employed: (1) methylation of hexaacetate using dimethyl sulphate and alkali in acetone medium, (2) methylation of gossypol with diazomethane in methyl alcoholic solution, (3) with methyl iodide and potassium carbonate in acetone solution and (4) with dimethyl sulphate and alkali. All the products had the same melting point, 130°, and gave analytical results corresponding to the hexamethyl ether. The methods which do not employ caustic alkali give samples which are less coloured. The methyl ether is unaffected by treatment with hot dilute sulphuric acid and hence does not seem to have the formula corresponding to the structure of glycosides.

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SYNTHETIC EXPERIMENTS IN THE BENZO-PYRONE SERIES

Part VI. Action of Aluminium Chloride on Angelicin, Psoralen and Related Compounds

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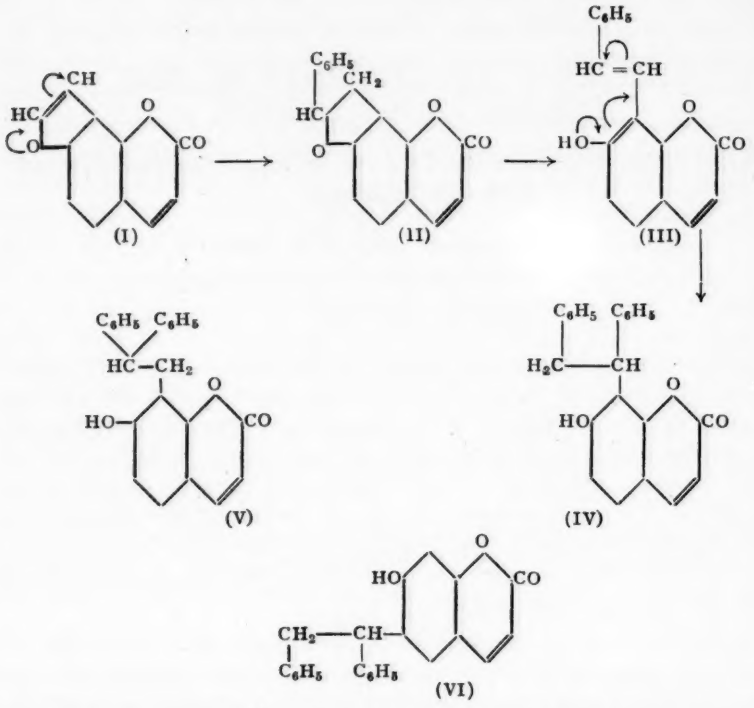
In a previous publication[1] it was shown that karanjin adds on a molecule of benzene or toluene in the presence of aluminium chloride, the addition taking place at the double-bond of the furan ring. Simpler flavones related to karanjin do not undergo this addition. Only demethylation of methoxyl groups takes place. If this observation could be proved to be general for all furan compounds, it will be useful for the synthesis of complex organic compounds and also for the purpose of diagnosing the presence of furan ring in such structures. The work has therefore been extended now to coumarin analogues.

Angelicin also called *iso*-psoralen (I) which has the constitution of coumarino-7 : 8-furan reacts very vigorously with aluminium chloride and benzene even in the cold. The crystalline product obtained is soluble in dilute alkali exhibiting fluorescence, characteristic of umbelliferone derivatives. This is sufficient indication that the furan ring has reacted and has opened out to produce a hydroxyl group at the 7-position and that the pyrone ring has remained unaffected. From the results of analysis of this product it is concluded that 2 molecules of benzene have taken part in the reaction and that the furan ring has been broken open. The constitution of the new substance, 8-diphenylethyl umbelliferone can be either IV or V and the former is preferred since the influence of the structural factors will favour the entry of the phenyl groups in this manner. The details are represented in the following formulæ.

Psoralen which has the constitution of coumarino-6 : 7-furan gives a definite crystalline product more easily on treatment with benzene and aluminium chloride. It is readily soluble in dilute alkali. Its solutions exhibit fluorescence and it forms a methyl ether. From these properties and from the results of analysis of this product and also of the methyl ether, it is concluded that as in the case of angelicin two molecules of benzene



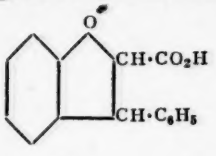
have taken part in the reaction and that the furan ring has been broken open so as to form 6-diphenylethylumbelliferone. Of two possible alternatives, constitution VI appears preferable for this product for the same reason as given in the case of the angelicin derivative.

Though toluene also reacts very vigorously with both psoralen and *iso*-psoralen, resulting amorphous sticky products could not be purified and crystallised.

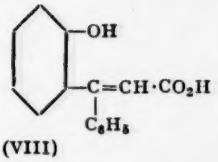
In order to obtain further evidence that the α-pyrone ring is not involved in the above reactions, simpler coumarins were next studied. Coumarin itself undergoes no change. Obviously the pyrone double-bond is not sufficiently anionoid to enter into the reaction. It seems to be strongly cationoid with the carbon atom in position 4 exhibiting cationoid activity. As could be expected 6-nitrocoumarin also undergoes no change. Since a hydroxyl or a methoxyl in the 7-position could reduce this cationoid activity, 7-methoxy-coumarin and 7-methoxy-4-methylcoumarin were carefully studied. Even in these cases no addition took place. In benzene and

toluene solution there was demethylation by aluminium chloride, the corresponding hydroxy-coumarins being formed. Even this did not take place when nitrobenzene was employed as solvent. In this respect there is resemblance to 7-methoxy-flavones.

It is therefore obvious that the pyrone ring does not undergo this addition with benzene or toluene. With a view to obtain more positive evidence that the furan ring is involved, simple coumarones have next been investigated. Coumarone itself undergoes rapid change into a solid resin in benzene or toluene. The same phenomenon is noticed in nitrobenzene. They seem to be products of polymerisation and such resins obtained by the action of dehydrating agents are well known. In this case polymerisation is so fast that the addition reaction seems to have little chance of taking place. Coumarilic acid should be much better owing to the modifying action of the carboxyl group. According to expectation it reacts with benzene smoothly to form 3-phenyl-dihydro-coumarilic acid (VII). The properties of this compound support this conclusion and differentiate it from the isomeric β-phenyl-coumaric acid (VIII) that may be produced if the dihydrofuran ring opened out.



(VII)



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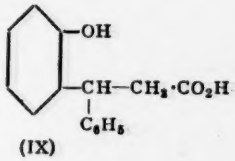

(IX)

It is interesting to record that coumaric acid undergoes addition of benzene satisfactorily to form β-phenyldihydrocoumaric acid (IX) and is thus sharply distinguished from coumarin. Similar difference in reactivity was also noted in their reaction with cyanoacetamide.[2] In this reaction with benzene coumaric acid closely resembles coumarilic acid.

Experimental

Addition of benzene to angelicin (iso-*psoralen*): 8-α: *β-diphenylethyl-umbelliferone.*

Iso-psoralen (0·2 g.) was dissolved in benzene (20 c.c.), powdered aluminium chloride (0·5 g.) added and the conical flask was well stoppered and shaken for about 4 hours at room temperature. Dilute hydrochloric acid (1 : 1) was then added and the benzene was removed by steam distillation. The viscous liquid product in the distilling flask set to a solid on cooling. On repeated crystallisation from alcohol or acetone, it gave

glistening micacious plates, melting at 205–6°. (Found: C, 80·4; H, 5·6; mol.wt. by Rast's Method 337. $C_{11}H_6O_3 + 2C_6H_6$ requires C, 80·7; H, 5·3%; mol.wt., 342. $C_{11}H_6O_3 + C_6H_6$ requires C, 77·3; H, 4·5%; mol.wt., 264. It dissolved in dilute alkali and the solution exhibited a blue fluorescence. The solution in concentrated sulphuric acid emitted a bright violet fluorescence.

Addition of benzene to psoralen: 6-α: *β-diphenylethyl-umbelliferone.*

Psoralen (0·5 g.) was dissolved in benzene (25 c.c.), powdered anhydrous aluminium chloride (1·0 g.) added and the mixture refluxed for 35–40 minutes. It was then cooled, the solvent decanted into another flask and evaporated to dryness. After treatment with dilute hydrochloric acid the product from both the flasks was collected on one filter and recrystallised from alcohol. Colourless rectangular plates, melting at 259–60° were thus obtained. Yield 0·2 g. Its solution in dilute alkali gave a bright blue fluorescence and in concentrated sulphuric acid a bright violet fluorescence. (Found: C, 80·6; H, 5·8; mol.wt. by Rast's method 333. $C_{11}H_6O_3+2C_6H_6$ requires C, 80·7; H, 5·3%; mol.wt., 342). The above compound was methylated by treating with methyl iodide and anhydrous potassium carbonate in acetone solution and refluxing for 6 hours. The methyl ether was obtained after recrystallisation from alcohol in the form of soft fibres melting at 172–73°. It was insoluble in dilute alkali but dissolved in concentrated sulphuric acid exhibiting violet fluorescence as in the case of the unmethylated compound. (Found: C, 80·7; H, 5·9; OCH_3, 8·9; $C_{24}H_{20}O_3$ requires C, 80·9; H, 5·6; OCH_3, 8·7%.)

To Coumarilic acid: 3-*phenyl-dihydrocoumarilic acid.*—A suspension of coumarilic acid (0·5 g.) in benzene (15 c.c.) was treated with aluminium chloride (1·0 g.) and refluxed for about 45 minutes, when the acid gradually went into solution. Finally the mixture was cooled, treated with dilute hydrochloric acid and the benzene removed by steam distillation. The solid product thus isolated crystallised from alcohol in needles melting at 143–4°. Yield 0·5 g. It gave no colour with ferric chloride. It did not decolourise a solution of bromine in acetic acid thus showing that there was no unsaturation and that the ring had not been opened. (Found: C, 75·0; H, 4·6; mol. wt., 245. $C_{15}H_{12}O_3$ requires C, 75·0; H. 5·0; mol. wt., 240.)

To Coumaric acid: *β-phenyl-dihydrocoumaric acid.*

Coumaric acid (0·5 g.) with the same treatment as above gave a product which crystallised from alcohol in rectangular plates. It melted at 152–53°,

and the mixed melting point with the coumarilic acid-benzene compound was lower than that of the two. It did not decolourise a solution of bromine in acetic acid and gave no colour with ferric chloride. Yield almost quantitative. (Found: C, 74·9; H, 6·2; mol. wt., 230; $C_{15}H_{14}O_3$ requires C, 74·4; H, 5·8%; mol. wt., 242.)

Demethylation of 7-methoxy 4-methyl-coumarin.

(*i*) *In benzene solution.*—7-Methoxy-4-methyl-coumarin (0·5 g.) was dissolved in dry benzene (20 c.c.), powdered anhydrous aluminium chloride (1 g.) added and heated gently under reflux on a water-bath (70–75°) for about 30 minutes. It was then cooled, the solution decanted into another flask and evaporated to dryness. 10 c.c. of dilute hydrochloric acid (1 : 1) was added to each of the two flasks to decompose the aluminium chloride and the resulting precipitates were collected together on the same filter. On recrystallisation, the product yielded long plates melting at 185°. The mixed melting point with a sample of 4-methyl-umbelliferone was unaltered. Yield 0·4 g.

(*ii*) *In toluene solution.*—The procedure was similar to the above except that since in place of benzene, toluene (20 c.c.) was used, it was finally removed by steam distillation. The product was recrystallised from alcohol and found to be identical with 4-methyl umbelliferone.

The behaviour of 7-methoxy-coumarin was the same as that of the 4-methyl compound under the above conditions.

Polymerisation of Coumarone

(*i*) *In benzene solution.*—Coumarone (10 drops) was dissolved in benzene (10 c.c.) and powdered aluminium chloride (1 g.) added. The mixture was shaken for about 2 hours, when the solution gradually turned to a deep purple colour and deposited a solid. It was filtered, digested with hydrochloric acid to remove any aluminium chloride and again filtered. The product was a white amorphous solid insoluble in all ordinary organic solvents.

(*ii*) *In nitrobenzene solution.*—The above experiment was repeated using nitrobenzene instead of benzene. Here also the solution gradually turned deep purple but no solid was deposited in two hours as in the above experiment. On keeping overnight, however, the whole solution set to a jelly. This was treated with hydrochloric acid and steam-distilled to remove nitrobenzene. A brown amorphous solid insoluble in the common organic solvents was thus obtained.

Summary

Angelicin and psoralen combine with benzene in the presence of aluminium chloride to form 8 or 6-α : β-diphenyl-ethylumbelliferone. Two molecules of benzene add on and the furan ring is opened out. That the coumarin ring is not involved and that the furan ring is the active centre are confirmed by the following observations: (1) Coumarin and 6-nitro-coumarin are unaffected; (2) umbelliferone and 4-methyl-umbelliferone methyl ether undergo simple demethylation; (3) coumarone undergoes polymerisation too vigorously to condense with benzene; (4) coumarilic acid undergoes addition with one molecule of benzene smoothly. Coumaric acid resembles coumarilic acid in regard to this reaction (addition) and differs from coumarin.

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CHEMICAL EXAMINATION OF THE ESSENTIAL OIL DERIVED FROM THE SEEDS OF *CARUM ROXBURGHIANUM* BENTH.

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Carum Roxburghianum Benth. is a low annual herb belonging to the Natural Order of Umbelliferæ. It grows abundantly throughout the Gangetic plains and also in the Central Provinces and in Hyderabad in Deccan. It is known in Hindi as " Ajmud " and in Bengali as " Shah Jira " or " Randhuni ", and is one of the lesser known spices cultivated in India for the flavouring of food. The seeds are very difficult to distinguish from ordinary *Caraway* or " Jira " seeds except by their very different flavours, so very closely similar are their external appearances. The corresponding plants also look almost identical with each other. The plants grow during the cold season and the seeds are ready for harvesting by the end of March.

Apart from their use as a spice in ordinary food preparations, they are also used as flavouring materials in various Achars, Chutneys and Preserves. They are also one of the constituents of numerous " curry powders " often sold in the market. The seeds are also highly medicinal. According to Kirtikar and Basu,[1] the seeds are useful in hiccup, vomiting and pain in the bladder. They form an ingredient of carminative and stimulant preparations and are very useful in dyspepsia and flatulence.

In view of the great medicinal importance of the seeds and their economic value, it was thought desirable to undertake the chemical examination of the essential oil contained in them which is undoubtedly the active principle of the material. No detailed investigation appears to have been made in this subject upto this time.

The essential oil is very easily obtained from the seeds by steam distillation in an yield of 2·5 per cent. Further examination of the oil resolved it into a number of different constituents, amongst which the major ones have been found to be d-*limonene*, *α-terpinene* and dl-*piperitone*. Amongst the minor constituents, the following have been definitely identified : d-*linalool*, dl-*terpineol*, *thymol*, *thymoquinol*, p-*isopropyl-benzoic acid* and a

Ketonic acid $C_{10}H_{14}O_3$ of unknown constitution. Traces of Cuminol have also been found to be present.

Experimental

20 Kgs. of the crushed seeds were submitted to distillation in steam from a large copper still fitted with a tinned funnel condenser and an automatic trap for the separation of the essential oil from the aqueous distillate. The oil recovered from the trap was dried with anhydrous magnesium sulphate and filtered. 520 Gms. of the dry essential oil were thus obtained, thereby giving an yield of about 2·5 per cent. on the weight of the seeds. The following table gives the properties of the oil:

Table I

Chemical and Physical Properties of the Essential Oil

Colour of the oil	Greenish-yellow
Sp. Gr. at 20° C.	0·9488
Refractive index at 20° C.	1·4880
Optical rotation at 33° C.	+25·5°
Acid value	4·9
Saponification value	49·1
Saponification value after acetylation	74·2

300 c.c. of the essential oil were distilled at the ordinary pressure through a Young's column, and the different fractions obtained at various temperatures refractionated through suitable fractionating columns for a number of times until the following ultimate fractions were obtained :

TABLE II

Fractionation of the essential oil

Fraction No.	Boiling range (° C.)	Volume of distillate (c.c.)	Sp. Gr. at 20° C.	Refractive index at 20° C.	Optical rotation at 30° C.	Per cent. yield
1	170–80	162	0·8488	1·4716	+92·9	54·0
2	180–90	9	0·8498	1·4726	+65·7	3·0
3	200–10	14	0·8748	1·4716	+26·5	4·7
4	210–20	17	0·9408	1·4836	+ 5·0	5·7
5	220–30	32	0·9405	1·4876	− 1·5	10·7
6	230–40	21	0·9766	1·4906	± 0	7·0
7	240–50	13	0·9691	1·4926	± 0	4·3
8	250–60	14	0·9750	1·4966	± 0	4·7
9	Residue	13	0·9733	1·4966	± 0	4·3
10	Loss by distillations	5	..	..	..	1·7

Chemical Examination of the Various Fractions

Fraction No. 1.—This was found to be an unsaturated hydrocarbon with a strong smell resembling limonene. On further examination it was found to be a mixture of *d*-limonene and α-terpinene in the proportion of approximately 65 : 35. It gave a brilliant green coloration on treatment with nitrous acid in accordance with Gildemeister's[2] directions, and the reaction product on standing for a long time yielded only relatively small proportions of colourless needles melting at 155° C., which were found to be α-terpinene nitrosite. The comparatively small yield of the nitrosite and also the fact that on treatment with bromine in glacial acetic acid the fraction gave only liquid bromine addition products and both hydrogen chloride and nitrosyl chloride failed to give any crystalline derivative, led to the suspicion that the fraction in question must naturally be a mixture of α-terpinene with a much larger proportion of some other hydrocarbon having a similar boiling point, which could evidently be limonene or dipentene. On account of the impossibility of separating the two products by physical methods, the α-terpinene in the mixture had to be destroyed by treatment with cold chromic acid in accordance with Beckmann's[3] method, and the remaining hydrocarbon after purification was found to be *d*-limonene (b.p. 176–78° C., $D_{20}^{\circ} = 0{\cdot}8495$, $n_D^{20^\circ} = 1{\cdot}4760$, $D^{30^\circ} = +120{\cdot}5^\circ$). It readily gave a tetrabromide with bromine in glacial acetic acid melting at 104° C.

Fraction No. 2.—This was found to be mainly *d*-limonene mixed with dipentene and α-terpinene. With bromine in acetic acid, it readily yielded the tetrabromide melting at 104° C. and with nitrous acid it gave the bright green colour reaction of terpinene, but the yield of the crystalline nitrosite was very little. On destruction of the α-terpinene in the mixture with cold chromic acid, the residue was found to be a mixture of dipentene and limonene only. The proportion of α-terpinene in the mixture was approximately 15 per cent. but that of the other two components could not be determined.

Fraction No. 3.—This was found be to *d*-linalool. The phenylurethane derivative prepared in the usual manner melted at 65° C.

Fraction No. 4.—This was identified to be terpineol. The nitroso-chloride prepared by the usual methods melted at 110–12° C., and the nitrolpiperidide obtained by the action of piperidine on the former melted at 155–56° C.

Fraction No. 5.—There was considerable difficulty in the identification of this fraction which was found to be ketonic in nature. It gave an oxime

melting at 117–18° C. and a semicarbazone melting at 228–29° C. It had a strong smell resembling old eucalyptus oil. A crystalline potassium bisulphite compound was obtained by the action of potassium metabisulphite in hot water. The substance was ultimately identified to be *dl*-piperitone. It gave thymol on oxidation with ferric chloride in glacial acetic acid. (Oxime: Found N = 8·0 ; $C_{10}H_{14}NOH$ requires N = 8·3 per cent. Semicarbazone: Found N = 20·5 ; C_{10} $H_{14}NNHCONH_2$ requires N = 20·09 per cent.)

Fraction No. 6.—This was found to be acidic in reaction. It was extracted with 5 per cent. aqueous sodium hydroxide solution and the aqueous layer after saturation with carbon dioxide, extracted with ether. The ethereal extract on complete evaporation of the solvent yielded an oil smelling strongly of thymol and on standing for three days in the refrigerator deposited a small quantity of colourless woolly needles. These were separated from the oily mother-liquor on a porous plate and on recrystallisation from hot water melted at 140° C. These were identified to be thymoquinol by direct comparison with a synthetic specimen. The yield was 0·7 g.

The oily mother-liquor from the thymoquinol was extracted from the porous plate by ether and on evaporation of the solvent a light yellow liquid was obtained which did not crystallise even on prolonged standing at the ordinary temperature. On distillation however, the major fraction which boiled at 230–35° C. solidified in the condenser as a colourless crystalline mass which melted at 49° C. This was identified to be thymol by the preparation of the nitroso derivative which melted at 164° C. The yield was 4·5 gm.

The aqueous mother-liquor from the ethereal extract mentioned above on acidification with dilute hydrochloric acid gave a colourless crystalline precipitate which on recrystallisation from dilute alcohol was obtained in the form of long glistening needles melting at 114–15° C. This was identified to be *p*-isopropylbenzoic acid or cumic acid by direct comparison with an authentic specimen. Apparently this acid must have been produced by the oxidation of the corresponding aldehyde or *cuminol*, traces of which were found to be present in the original essential oil. The yield obtained was 1·2 gm.

The residue of the original fraction No. 6 remaining behind after extraction with aqueous alkali (9·5 c.c.) was washed with water, dried and distilled. The major fraction which passed over at 232°–35° C. was found to be piperitone by formation of the oxime and the semicarbazone already described. Traces of cuminol could also be detected in the tail fractions, but it could not be isolated either as such or in the form of its derivatives.

Fraction No. 7.—This had already partially solidified with formation of a few thick prismatic crystals. The crystals were separated from the mother-liquor and recrystallised from dilute alcohol, when they were obtained in the form of glistening prisms melting at 105–06° C. They could not be definitely identified, but they appear to be those of the ketonic acid $C_{10}H_{14}O_3$ described by Wallach and Hallstein[4] and obtained by the oxidation of piperitone. These authors have also recorded the melting point of 105–06° C. (Found : C = 65·53 ; H = 7·92 ; $C_{10}H_{14}O_3$ requires C = 65·93 ; H = 7·69 per cent.)

The mother-liquor from the above crystalline deposit was found to be acidic in reaction and on extraction with aqueous caustic soda and proceeding as already described under Fraction No. 6, a small quantity of thymol and a further small quantity of the above-mentioned acid melting at 105-06° C. were obtained. The neutral oil after removal of the acidic constituents was found to be an ester or a mixture of esters with a saponification value of 210, but it could not be definitely identified. Traces of cuminol were also found in the substance.

Fraction No. 8.—This was also found to be acidic in reaction and from this also by extraction with alkali, small quantities of thymol and the previously mentioned ketonic acid could be isolated. But the major fraction of the substance consisted of esters together with high boiling hydrocarbons which could not be identified.

Fraction No. 9.—This was found to be a dark brown viscous liquid with a few crystals embedded in the sticky medium. It could not be worked up or identified.

Summary and Conclusions

1. The essential oil of *Carum Roxburghianum* Benth. seeds was obtained in an yield of 2·5 per cent. by steam distillation.

2. Further examination of the oil revealed that it contained the following constituents :

d-limonene	35·1 per cent.
d-limonene and dipentene mixture ..	2·5 ,,
α-terpinene	19·4 ,,
d-linalool	4·7 ,,
dl-terpineol	5·7 ,,
thymoquinol	0·2 ,,
thymol	1·7 ,,
dl-piperitone	13·6 ,,

p-Isopropylbenzoic acid	.. ..	0·4 per cent.
Cuminol	..	traces
Unidentified ketonic acid $C_{10}H_{14}O_3$	..	1·0 „
Unidentified esters	..	5·9 „
Unidentified	..	9·8 „

One of the authors (B.K.M.) wishes to express his indebtedness and thanks to the Kanta Prasad Research Trust of the Allahabad University for a scholarship which enabled him to take part in this investigation.

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PREPARATION OF β, 2-FURYL ACRYLIC ACID

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(Communicated by Lt.-Col. S. S. Sokhey, M.A., M.D., I.M.S.)

Despite the relatively long history of furan compounds, dating from the discovery of furoic acid about 160 years ago, there is an astonishing paucity of information about them when compared to other hetrocyclic types. A large portion of research in this field has centred round furfural, discovered[1] over a century back accidentally, or its numerous derivatives. The ready and spontaneous decomposition of many furan compounds and the ready formation of apparently intractable oils, resins, tars and chars may, perhaps, account for past sporadic investigations which culminated in a feeling on the part of some that reactions with labile furan types were extremely difficult and virtually impossible. Recent years have, however, witnessed many furan derivatives rising to prominence. They have come to play a part in industry[2] as plastics, synthetic resins, industrial solvents, etc., and in the group of synthetic drugs such as antiseptics,[3] hypnotics or anæsthetics,[4] sympathomimetics,[5] mydriatics[6] physiologically active compounds of the pyrazolone series,[7] and as isoquinoline derivatives or analgesics.[8]

The preparation of β, 2-furyl acrylic acid in quantity has been of especial interest in connection with studies[9] on the synthesis of possible analgesics. It may be well to recall, at this stage, that furylacrylic acid, although its pharmacology[10] has been investigated without any definite findings, forms an important intermediate for the synthesis of a promising local anesthetic,[11] *viz.*, 1-piperidino 2, 3-diol difuran acrylate. A scrutiny of the literature revealed that a few reports[12] had in the past appeared on the preparation of the acid. Out of these, the one entitled to serious consideration, from the point of view of a profitable preparative method, seems to be that of Johnson,[13] who has developed a modification of the Perkin procedure. This communication is concerned with a method possessing certain advantages in respect of shortness of time, cost of the materials involved and grade purity of the finished product, over those already in existence for the large-scale productions of furyl acrylic acid.

The present procedure is essentially founded on the pyridine trace method[14] as elaborated by Pandya and his collaborators. Various conditions were tried out in order to ascertain the factors influencing maximum yields and purity of the acid. The data obtained are presented in tabular form.

No.	Furfural	Malonic Acid	Pyridine	Piperidine	Period of heating at 100°	Yield and M.P. of acrylic acid	Remarks
1	24 g. (15 c.c. 1 mol.)	26 g. (1 mol.)	1 c.c. (0·05 mol.)	..	4 hrs.	..	Tarry product : not worked up.
2	24 g.	26 g.	3 c.c. (0·15 mol.)	..	4 hrs.	17·4 g., 138°	Tan coloured, yielding 12·5 g. pure acid.
3	24 g.	26 g.	6 c.c. (0·30 mol.)	..	2 hrs.	21·0 g., 139°	Slightly pale product
4	24 g.	26 g.	6 c.c.	..	4 hrs.	21·5 g., 139°	do.
5	24 g.	26 g.	6 c.c.	2 drops	4 hrs.	21·6 g., 139–40°	do.
6	24 g.	26 g.	12 c.c. (0·60 mol.)	..	2 hrs.	22·0 g., 141°	Almost white product
7	24 g.	26 g.	12 c.c.	..	4 hrs.	22·0 g., 141°	do.
8	24 g.	26 g.	20 c.c. (1 mol.)	..	1 hr.	19·5 g., 140–41°	do.
9	24 g.	26 g.	20 c.c.	..	2 hrs.	22·0 g., 141°	do.
10	24 g.	26 g.	20 c.c.	..	4 hrs.	22·0 g., 141°	do.
11	24 g.	26 g.	12 c.c. (0·60 mol.)	..	2 hrs.	21·9 g., 141°	do.
12	96 g. (60 c.c.)	104 g.	48 c.c.	..	2 hrs.	92·0 g., 141°	do.
13	96 g.	104 g.	48 c.c.	..	2 hrs.	91·0 g., 141°	do.
14	96 g.	104 g.	48 c.c.	..	2 hrs.	92·0 g., 141°	do.
15	192 g.	208 g.	96 c.c.	..	2 hrs.	184·0 g., 141°	do.

From the practical standpoint of convenience, economy and purity of the resulting product, choice was made of experiment No. 6 as meriting detailed study and investigation of the possibility of its development into a preparative method. This expectation has now been fully realised: allowing even for loss in recrystallisation, the average yield of furyl acrylic acid from numerous experiments (Nos. 12–15) works out to about 65 per cent. of the theoretical amount and compares favourably with 56 per cent. for a similar grade of acid obtainable by the method of Johnson.[13]

Experimental

The furfural used was an ordinary commercial variety, which was subjected to a single distillation and stored in a brown bottle, as also the malonic acid, marketed as "practical" quality by Messrs. Eastman Kodak Co.; the latter was, however, dried at 100° for 2 hours. The pyridine

required in these experiments was a commercial brand and was dried over solid potash.

The aldehyde (1 mol.), malonic acid (1 mol.) and the requisite amount of pyridine were brought together in a suitable vessel and the mixture heated on the boiling water-bath for the desired period. The reaction-mixture was diluted, a slight excess of dilute ammonium hydroxide added and the filtrate acidified with excess of hydrochloric acid. The separated product was filtered after cooling, washed and dried between filter-papers.

β, 2-Furyl acrylic acid.—In a 1 litre round-bottomed flask, fitted with a reflux condenser, were brought together furfural (192 g., 120 c.c., 2mols.), malonic acid (208 g., 2 mols.) and pyridine (96 c.c., 1·2 mols.) and the mixture heated on the boiling water-bath for 2 hours, cooled and diluted with water (200 c.c.). Enough liquor ammonia was added in order to produce a clear solution, filtered through a fluted filter-paper and the paper washed with three 80 c.c. portions of water. The filtrate was treated, without external cooling, with an excess of dilute (1 : 1-) hydrochloric acid. The mixture was cooled at the tap, allowed to stand at 0° for atleast 1 hour, the separated acid filtered, washed on the filter with four lots (100 c.c. each) of ice water and dried between filter-papers.

Furyl acrylic acid, obtained as above, is crystalline (needles), nearly white and melts at 141°; yield 184 g., or 66–67 per cent.

The acid is of a high order of purity and can be utilised straightaway for further synthetic operations. If, however, a recrystallisation is desired, it is best effected from dilute alcohol with the addition of one-twentieth its weight of decolourising carbon. It is then obtained, on slow cooling with an approximate loss of 2 per cent., as slightly pale and several-inches-long needles, melting at 141°.

Summary

The factors influencing optimum yields and purity of furyl acrylic acid by the condensation of furfural and malonic acid in the presence of pyridine have been investigated.

A rapid and elegant preparative method for β, 2-furyl acrylic acid of a high degree of purity has been worked out.

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